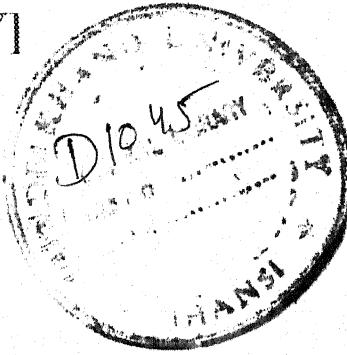


Oxygen saturation and analgesic effects in different pre-emptive analgesic regimens (a comparative clinical study)

THESIS
FOR
DOCTOR OF MEDICINE
[ANAESTHESIOLOGY]

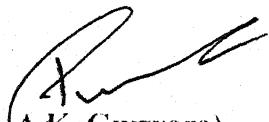


**BUNDELKHAND UNIVERSITY
JHANSI [U.P.]**

CERTIFICATE

This is to certify that the work entitled "*Oxygen saturation and analgesic effects in different preemptive analgesic regimens. (A comparative clinical study)*", which is being submitted as a thesis for MD Anaesthesiology by Dr. Mridula Agrawal, has been carried out in the department of Anaesthesiology, M.L.B. Medical College, Jhansi.

She has fulfilled the necessary stay in the department as required by the regulation of the Bundelkhand University, Jhansi.



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CERTIFICATE

This is to certify that the work entitled "*Oxygen saturation and analgesic effects in different pre-emptive analgesic regimen (a comparative clinical study)*" which is being submitted a thesis for M.D. Anaesthesiology by Dr. Mridula Agrawal has been carried out under my direct supervision and guidance.

The technique and statistical methods used were undertaken by the candidate herself. The same were checked by me from time to time.



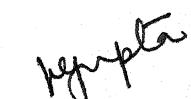
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Acknowledgement

"oh my God, to him I pray
increase my knowledge day by day"

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I thank you all.

Mridula Agrawal.

(MRIDULA AGRAWAL)

Dated :- 5.9.2001.

This piece of work
is dedicated to
My husband
Dr. Shailesh and my son Shubh

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INTRODUCTION

INTRODUCTION

The international association for the study of pain has defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”. The interpretation of pain is subjective. Pain is an unpleasant sensation localized to a part of the body. So pain is not only pain, but also an alarm for body injury.

MacInnes, after being subjected to surgery, described post operative pain as “the grave defeat of english pubic hospital treatment’ which is a cruel and callous disgrace’. Donald, a professor of obstetric described his pain after open heart surgery as experience worst ever.

Post operative pain does not directly cause death but so many adverse effects and morbidity that overall surgical outcome is negatively affected.

Pain causes lack of sleep and poor sleep patterns. The sleep deprivation is detrimental to healing process and effects mental state leading to increased pain scores and increased levels of anxiety. Stimulation of sympathetic nervous system by pain leads to an increase in blood pressure, heart rate and inotropy. The resultant increase in oxygen demand may lead to ischaemia if there is no marked increase in supply. Sympathetic activation leads to coronary vasoconstriction. These changes are possible without a change in heart rate or blood pressure and may be responsible for silent ischaemia. Once ischaemia develops, a secondary sympathetically mediated rise in heart rate and blood pressure exacerbate the problem. Pain after thoracic and abdominal surgery or trauma may lead to diaphragmatic splinting and reduced functional residual capacity. Resulting impaired respiratory function may lead to hypoxaemia, atelectasis, lobar collapse and pneumonia. Patients specially at risk include those with pre-existing respiratory disease, obesity and old age. Surgery and trauma result in a hypercoaguable state that is thought to be mediated, at least in part, by the stress response and increased sympathetic activity. Pain leads to gastric stasis and may delay enteral feeding. This is important consequences, as early feeding has been demonstrated to improve wound healing and reduce septic complications. The reason why pain leads to stasis are unclear, but it is possible that abdominal pain activates a spinal reflex arc. Also increased response to pain leads to inhibition of co-ordinated bowel activity: Surgical stress elicits a

metabolic response via the activation of sympathetic and somatic nervous system, and via humoral factors released at the site of local trauma. The stress response is characterized by hypermetabolism, mobilization of substrates from energy stores and massive muscle breakdown. Mediators of stress response are known to also be potent immunosuppressor. Both cell mediated and humoral systems are affected. Analgesia, by reducing the stress response, may attenuate these changes in immune function.

The pain relief is very important aspect of surgical outcome. Given the leadership of anaesthesiology in raising awareness about the issue of pain management and the enormous effort put forth over the five decades to create pain clinics and pain management centres, our specially has worked and created special qualification in pain management.

The traditional approach to post operative analgesia is to begin therapy when surgery is completed and pain is experienced. But one aim of modern anaesthesia is to ensure that patient have surgery without pain, awake from anaesthesia with excellent pain control and maintains this control throughout the period of convalescence. The aim is to prevent rather than treat severe post operative pain. This concept is known as “pre-emptive analgesia”. By this we prevent the establishment of altered central processing which amplifies post operative pain. Intense noxious stimulation can sensitize portions of central nervous system to subsequent input. Such stimulation in form of surgical incision, may lead to functional changes in the dorsal horn of spinal cord and other consequences that later cause post operative pain to be perceived as more painful than it would otherwise have been. So to prevent all these consequences, concept of pre-emptive analgesia is gaining popularity day by day. Some studies have shown the encouraging results of this approach to post-operative analgesia but some also have shown this approach to be ineffective.

There are various modalities of post – operative pain relief. The mainstay for post-operative pain relief since ancient time are systemic opioids. They provide good, effective and long duration of pain relief. But narcotics bring with them some undesired side effects such as nausea, vomiting, dysphoria, problem of addiction, depression of cough reflex and respiration causing hypoventilation and retention of secretions leading to arterial hypoxaemia and atelectasis and pneumonia.

Fentanyl is short acting, 100 times more potent than morphine in analgesic property, highly lipid soluble with good cardio vascular stability and less respiratory depression. "Gardocki, J.P., Yelonski, J. have studied the pharmacological actions of Fentanyl Citrate". "Van wijngaarden 1, Soudijn W", studied the metabolism and excretion of the analgesic fentanyl "Downes, J.J. Kemp, R.A., Lambertsen, C.J." worked on the magnitude and duration of respiratory depression due to fentanyl and meperidine in man. "Willens JS, Myslinski NR", (Heart Lung 1993; 22:239-251) studied the pharmacodynamics and pharmakokinetics and clinical uses of fentanyl, sufentanil and alfentanil.

Various nerveblocks, NSAIDS, inhalational agents (when the patient require post-operative mechanical ventilation), transcutaneous nerve stimulation (TENS), local infiltration techniques, all are effective methods to provide post operative analgesia.

Local infiltration technique is useful as single subcutaneous injection of local anaesthetic can produce sustained pain relief for a period of hours on incision line without altering vital parameters, but its limitation is that, it does not reduce dull aching type visceral pain so is effective only in operations where viscera handling is minimum such as herniorrhaphy appendectomy etc. and also it can delay in wound healing.

The discovery of opiate receptor in the brain and spinal cord, the finding that intrathecal & epidural morphine produces intense analgesia in animals and man have raised exciting possibilities in the treatment of post operative pain. Production of analgesia without the loss of other sensations, with minimum central depression and without the consequences of autonomic blockade by using this technique has been well documented.

Opioid with local anaesthetic mixture have been used many a times for post operative pain relief, combination of these two provide synergistic analgesic action of local anaesthetic and opioid and both of these decrease dose of each other so that also minimizing side effects.

Pain relief after surgical procedures has always been of great concern to clinicians, although a larger number of analgesic agents are available for management of pain , much unnecessary suffering occurs because doctors and nurses are in impression that repeated administration of narcotic drugs to control pain can lead to addiction (Lasagna, 1964), and

also all patients are not able to tell truly about their pain and analgesic requirements so it is a better approach to provide analgesic before the pain starts, that is, to use pre-emptive analgesic regimens.

Though much has been said about the pre-emptive analgesia for post operative pain relief but which route should be chosen so as to have maximum pain relief along with minimum oxygen desaturation is still debatable. Therefore it was decided to evaluate the three different routes i.e. intravenous opioid, subcutaneous infiltration of bupivacaine and epidural opioids for the relief ^{of} post operative pain along with its effect on arterial oxygen saturation as an index of respiratory depression.

REVIEW

OF

LITERATURE

REVIEW OF LITERATURE

The use of analgesics goes back to 2250 BC, in the maiden record of the Babylonian clay tablet from Nippus. The analgesic pills were first referred by census in his De Medicone (First Century A.D.). The importance of the central nervous system for pain was realized by Galen (Second Century A.D.), who performed experimental cordotomy. William Harvey, overwhelmed by his circulation discovery, announced heart to be the sole culprit for pain. A step forward was the concept of "delicate threads" for the transmission of sensation, reproduced by Descartes in 1644. Contrary to all beliefs, Chinese consider the evil of pain as recent guest, easy to expel out by acupuncture through 365 suitable points.

With the dawn of nineteenth century, the actual strategy of pain control grew up from its childhood. Charles Bell (1811) laid his emphasis on dorsal roots of the spinal nerves, being distinct from ventral roots in function. Johanneus Muller (1816) expounded the theory of specific nerve energies which was later disproved.

By the sunset of nineteenth century, pain perception was explained by three different ways in the form of emotional experience, intensive theory and specific sensory theory. Schiff (1848) ruled out the importance of touch and found pain a distinct entity. Blin (1884) separated pain & pressure spots over skin. Vonfrey (1894) histologically identified end organs for each sensation. Thus the concept of pain as a sensation got speed, further emphasized by strong in 1895.

The hallmark of pain control was the first demonstration of surgical anaesthesia at the Massachusetts General Hospital in October 1846 by William T.G. Morton. The isolation of morphine by Serturner in 1806, marked the onset of systemic analgesia. Bennett (1873) and Anrep (1878) demonstrated analgesic properties of Cocaine to advance regional anaesthesia. Abbe performed posterior rizotomy to introduce neuro-surgical technique for halt of pain.

POST-OPERATIVE PAIN : Pain after operation is largely a result of direct trauma to the tissues by surgery but may be aggravated by reflex muscular spasm, visceral distention, cough and movement. It is self limiting phenomenon, most severe during the first day after

surgery, diminishing over next 24 hours and minimal after 3 or 4 days (Wallace and Morris, 1975).

Plug and Bonica (1977) reviewed post-operative pain. After surgery, the total pain experience is produced by input from three sites of injury-the skin, the deep somatic structures and the involved viscera. The cutaneous component is characterized by sharp quality, is well localized and often is accompanied by a burning sensation. The deep somatic component produces diffuse, aching discomfort that is either felt locally or in an area of reference or both. The visceral component result is dull, aching pain of diffuse quality.

ADVERSE EFFECTS CAUSED BY POST – OPERATIVE PAIN :

1. ***Respiratory*** :- Surgery involving upper abdomen or thorax produces many pulmonary changes like reduced vital capacity, tidal volume, residual volume, functional residual capacity and forced one second expiratory volume. Painful surgical incision involving the upper abdomen result in a reflex mediated increase in tone of abdominal muscles during expiration and decrease in diaphragmatic function. The result is reduced pulmonary compliances, inability to breathe deeply or cough forcefully and in some cases it may lead to hypoxia, hypercarbia, retention of secretion, atelcetais & pneumonia.
2. ***Cardiovascular*** :- Pain causes stimulation of sympathetic neurons and subsequently tachycardia, increased stroke volume, cardiac work and myocardial oxygen consumption. The risk of myocardial ischaemia or infarction is increased. Also risk of deep vein thrombosis is increased as physical activity is decreased because of fear of pain.
3. ***Gastrointestinal and Urinary*** :- Ileus, nausea, vomiting following surgery can occur for a number of reasons that include non nocieptive impulses form viscera and somatic structure. Pain can also cause hypomotility of urethera and bladder and consequent difficulty with urination.
4. ***Neuroendocrine and Metabolic*** :- Supra segmental reflex response to pain result in increased sympathetic tone, hypothalamic stimulation, increased catecholamine and

catabolic hormone secretion like cortisol, ACTH, ADH, GH, C-AMP, Glucagon, aldosterone renin angiotensin II and decreased secretion of anabolic hormones like insulin, testosterone.

5. ***Coagulation*** :- Surgery and trauma result in a hyper coaguable state, that is thought to be mediated, at least in part by the stress response and increased sympathetic activity.
6. ***Immune function*** :- Mediators of stress response are also known to be potent immuno suppressor. Both cell mediated and humoral systems are affected. Analgine, by reducing the stress response, may attenuate these changes in immune function.
7. ***Psychological*** :- Pain causes lack of sleep and poor sleep patterns. This may lead to acute anxiety state, depression and many types of psychosis.

SEVERITY OF POST OPERATIVE PAIN :-

Bonica (1953) listed various factor which may influence the severity of post-operative pain as the personality of patient, age, sex, physical status, site of operation and surgical management.

Age :- Pratt and Welch (1955) reported that post-operative analgesic requirements lessened with increasing age. Parkhouse et al (1961) found a small but significant fall in analgesic requirements in patients over 50 years of age as compared to those under 50.

Sex :- Parkhouse et al (1961) found that analgesic requirements did not differ in patients of different sex groups, although female patients tended to receive the analgesic drugs earlier in post operative period.

Site of Operation :- Keats et al (1961) found no difference in total analgesic requirements of patients subjected to cholecystectomy, gastrectomy, colectomy, pneumonectomy or hysterectomy. Park house et al (1961) and Loan et al (1967) however, observed that analgesic requirements were more after upper abdominal surgery than after lower abdominal surgery.

Patients :- The intensity of pain after injury is lessened with heightened emotional activity of the subject.

Roe (1963) found that total opiate requirement could be considerably decreased by pre-operative conditioning of the patient coupled with constant post-operative encouragement and reassurance.

Premeditation and Anaesthesia :- The request for post-operative analgesic is delayed, although total requirement of analgesic remains unaffected by narcotic premedication. Pratt and Welch (1955) found no difference in post operative requirement of analgesics in two groups with morphine or barbiturate premedications.

Park house et al (1961) found that inhalational anaesthetics with mark analgesic properties decrease analgesic requirement and delay the request for first analgesia.

PAIN PATHWAYS

Pain is one of man's most compelling experience. It is an unpleasant sensation, which only the individual can appraise and as such is incapable of a satisfactory objective definition (Mershey and Spear, 1967). Sherrington (1906), has described pain as "the psychical adjunct to an imperative protective reflex." This concept certainly draws attention to the protective aspect of pain.

Although the nature of pain was recognized by the great Greek philosophers, the theory that the pain can be produced by intensive stimulation of any sensory organ, has been frequently discussed. The neuro-anatomical basis of pain sensibility has been unfolded in the past, following the discovery of sensory functions of the posterior spinal nerve roots and the existence of medullary pathways comparatively specialized for pain.

The receptor organs for pain are distributed throughout the body, but it is convenient from the clinical aspect to consider pain under the following headings.

- A. Superficial or cutaneous pain
- B. Deep pain (Muscular, Bones, Ligaments, Joints and Fascia)
- C. Visceral pain
- D. Referred pain
- E. Psychogenic or functional pain.

The physiological mechanisms and the neural pathway for reception, conduction and appreciation of painful stimuli, irrespective of the site of its origin, are same, and therefore the description that follows is common to all types of pain.

The neurophysiological mechanism can best be understood under the following headings.

- (i) ***Reception of Pain :-*** The superficial, deep and visceral tissues are supplied with the network of non-myelinated or poorly myelinated nerve fibres, responsible for the transmission of pain. These fibres respond to variety of external stimuli, example thermal, mechanical, electrical or chemical.

The exact nature of the response whether by direct excitation of bare nerve endings or by tissue damage with secondary release of pain producing substances, is not clearly understood.

Although Hardy and others (1951), by working with thermal energy, concluded, that the onset of pain coincided with the temperature at which alteration in urine protein started taking place. As a result they anticipated release of pain producing substance. But, Beecher (1956) rejected this theory and pointed out that extensive tissue damage can be produced without pain being experienced. He blames the level of anxiety as being responsible for the occurrence of pain. Wolf and Wolf (1958) consider that in such extensive injuries, coagulated serum, edema and devitalized tissue may shield the pain endings from noxious stimuli, moreover, damage to nerve terminals and fibres may desensitize traumatized tissues.

A pain producing substance, probably a polypeptide, has been detected by Armstrong and his co-workers (1957) in inflammatory exudates. They have also held several other substances, like histamine, acetylcholine, angiotonin, bradykinins, adenosine triphosphate, serotonin, hydrogen & potassium ions and 5 - hydroxytryptamine, responsible for producing pain (Armstrong et al., 1953). Recent evidence (Ferreira, 1972), suggests that prostaglandin E, sensitizes the pain receptor to stimuli such as pressure and also the action of chemical mediators.

(ii) ***Conduction of pain :*** Pain is conducted from the receptor site to the spinal cord, and thenceforth through various ascending pathways to the sensory cortex for its perception, by means of mixed nerves which act as transmitting cables.

These mixed nerves are collection of various types of fibres both myelinated and non-myelinated, and Gasser (1943), has classified these fibres into three broad groups, depending upon the diameter and the conduction velocity of nerve impulse.

The classification is as follows:

Terminology	Fibre	Diameter (in μm)	Conduction Speed (in meter / sec.)
Myelinated Somatic fibres	Alpha	20	120
	Beta		
	Gamma		
	Delta	3-4	16-30
	Epsilon	2	5
Myelinated Visceral fibres (Pre ganglionic autonomic)		3	3-15
Non myelinated Somatic Fibres C		2	0.52

This groups of fibres are responsible for the transmission of pain. These are –

- (a) the myelinated A delta fibres which have the diameter of 3-4 μm and conduct at the speed of about 35 meters / second.
- (b) The more slowly conducting C fibres which are unmyelinated, have a diameter of less than 2 μm , with a conduction velocity of 0.5 – 2 meter/sec.

The existence of both fast and slow neural pathway for conducting pain impulse to the central nervous system, is suggested by the occurrence of a double pain sensation, so called the ‘echo pain’. The term applies to the twin peaks of pain which may follow the brief pain stimulus to the skin. Landau and Bishop (1953), concluded from their experimental study that C fibres – pain had a delayed, burning and persistent character, while the one transmitted through delta fibres is sharp and pricking in nature.

(iii) Central nervous system :-

- (a) **Transmission in spinal Cord :-** All the primary sensory afferents have their cell bodies in the dorsal root ganglion of the spinal cord. Pain fibres enter the spinal cord via the dorsal root and then ascend or descend for one or two segments in the medial portion of

Lissauer's tract to enter the more ventrally placed dorsal horn. Medial portion of lissauer's tract carries excitatory fibres from adjacent roots, while lateral portion carries inhibitory fibres.

The second synapse is formed in the substantia gelatinosa at the tip of dorsal horn, after the fibres have traversed 1-3 segments. The axons of the second neuron cross the mid line in the anterior commissure to form the lateral spinothalamic tract, which ascends and terminates in the lateral nucleus of the thalamus.

The spinothalamic tract is characteristically divided into two –

- (a) The neospinothalamic tract – which arises from the dorsal horn, occupies the antero-lateral quadrant of the spinal cord. The axons terminate in the ventrobasal complex of the thalamus. This tract perceives the intensity of pain and localises it.
- (b) The paleospinothalamic tract – which originates from the dorsal horn, receives 'C' fibres input, crosses the anterior commissure and ascends in the spinal cord closely applied to, but more ventral than the neospinothalamic tract.

The fibres, after giving collaterals to the reticular formation of the brain stem, terminate in the central, lateral and intra-laminar nuclei of the Thalamus. This pathway transmits the arousal component of pain.

A third spinal ascending pathway which may play some role in the nociception, is the spino-reticular pathway which consists of projections from small myelinated and unmyelinated fibres in the dorsal horn, mostly ipsilaterally and to a lesser extent centro laterally. The fibres terminate in the brain stem reticular formation, particularly in pons and medulla.

The grey matter in the spinal cord is arranged in the form of 10 laminae. Lamina 10 is around the central canal, lamina 9 in the motor neuron while 7 and 8 are interneurons. The dorsal horn, as it is classically known as, is laminae 1-6. Laminae 1,2 and 3 form the substantia gelatinosa; 4,5 and 6 form the nucleus proprius with Clarke's column in 6. Lamina 1-6 receive the primary afferent neurons and the cells in each layer converge on the layers

below. Each lamina is activated by its own afferent neurons and a particular level of activity is achieved in this fashion (Sampson Lipton, 1976).

(c) Reticular system : The fibres originating in the brain stem reticular formation, receive input from several sources, including almost certainly, the paleospinothalamic and spino-reticular pathways; ascend in polysynaptic projection to the wide area of thalamus. This provides an alternative route for pain impulses to bombard a large area of the cerebral cortex. It is believed that stimuli following this pathway activate the cortex and help to maintain consciousness; this is probably a non-specific arousal mechanism.

(iv) ***Thalamus and the Sensory Cortex :-*** Consciousness of pain is experienced at the level of thalamus, which contains a series of nuclei; a number of these are known to be involved in the appreciation of pain. Ascending reticular fibres form two groups, one of which is distributed to the intralaminar nuclei of thalamus while the other passing to the hypothalamus. Spinothalamic tracts terminate in the posteriolateral ventral nuclei of thalamus before relaying onwards and the posterior column fibres also terminate in the thalamus. Thus it can be appreciated that all sensory fibres converge on the thalamus.

After relay in the thalamus the sensory fibers project into the – post – central gyrus in the cerebral cortex, maintaining the dermatomal arrangement of fibres. It is possible to map out a distorted image of the body in the cortex itself.

The relative importance of thalamus and cortex, in the perception of pain, is still disputed. Head (1920) believed that pain is experienced when nerve impulses arrive in appropriate path of thalamus and regarded it as the centre of consciousness for pain. Thalamic sensation is crude and poorly localized, while cortex is essential for localising and detecting variation in the intensity of pain. To ascribe sensation to the thalamus and perception to the cortex, is to take too narrow a view of a complex function inter – relationship. The conscious appreciation of pain appears to depend upon the widespread activity of intact cortex. It thus enables the individual to interpret and formulate his own personal reaction to a particular painful experience.

The intensity of pain, suffered, varies enormously with the personality, intelligence and culture of the individual. Emotional stress and anxiety adversely effect the pain response as also debility and fatigue .

(v) ***Descending pathway :-*** Descending pathways comprise of fibres which originate in the orbital frontal cortex and probably descend via cortico-spinal tract. The fibres which originate in the mid brain reticular formation and raphe nucleus of the medulla and descend via polysynaptic pathways, reach the dorsal horn to modulate input to all laminae of dorsal horn particularly lamina 5. These descending fibres may influence activity at the dorsal horn level via either pre or post synaptic contact and may be either facilitatory or inhibitory.

THEORIES OF PAIN

For pain transmission, perception and appreciation, three theories were put forward.

First was the specific pain theory in which it was postulated that there were specific pain receptors in the spinal cord and specialized nerves and pathways transmitted painful stimulation from periphery to spinal cord and from spinal cord to brain. It was believed that pain was perceived on a one – for – one basis.

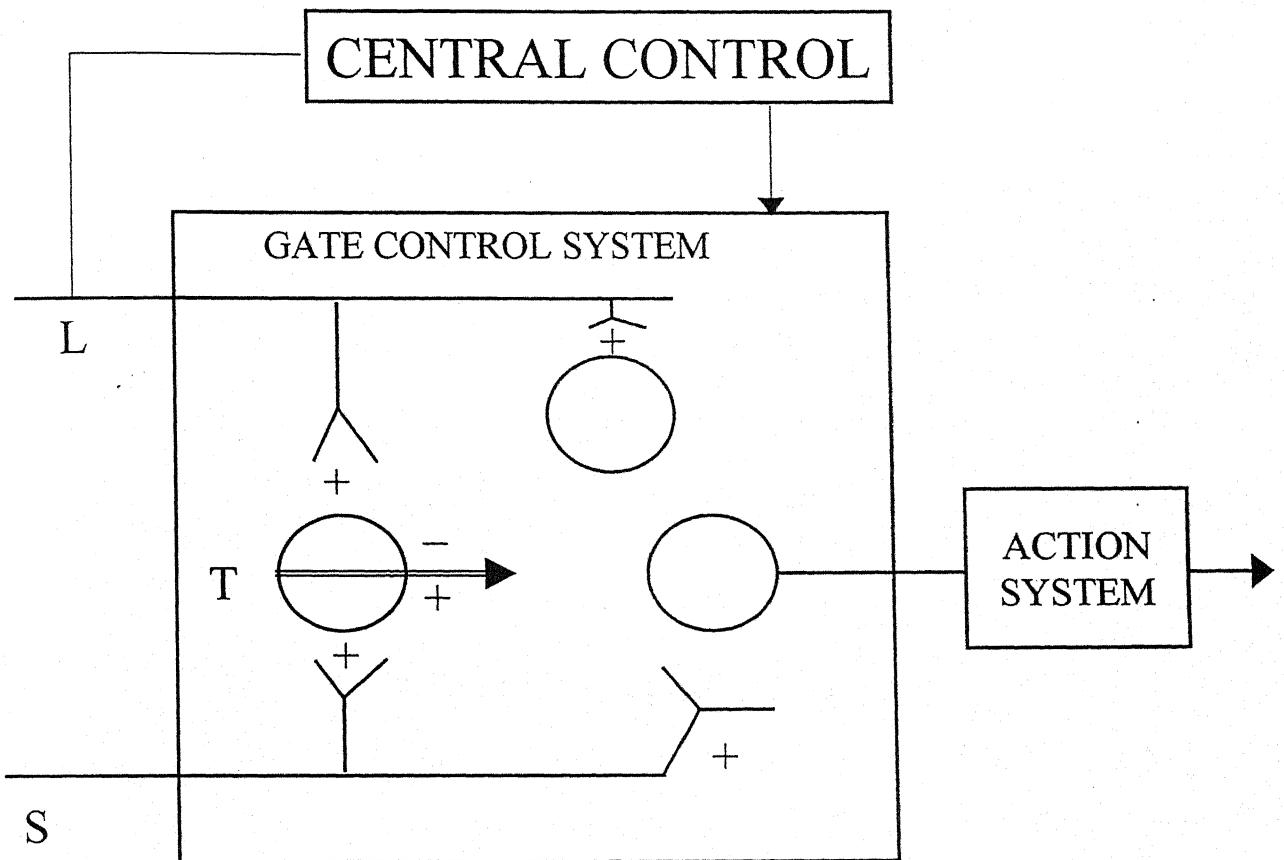
Second was the “pattern theory” in which it was postulated that pain sensation was coded in same fashion at the periphery as brain and that it was the patterns of frequency of strength of the electrical stimulation passing through nerve fibres and nerve cells which ultimately were interpreted as pain.

Most recent and still accepted is the third “Gate control theory” proposed by Melzack and Wall (1965), expanded in the form of a model by Casey and Melzock (1967) schematically represented in the diagram, on next page.

In this theory, it is suggested that the sensory input from the stress is modulated by a gate control system before its eventual perception as pain. The sensory impulses from the skin are distributed to three systems in the spinal cord, the tracts of the dorsal columns for onward transmission to the brain, the cells of the substantia gelatinosa and the first central transmission (T) cells in the dorsal horn which transmit sensory information to high centres.

The substantia gelatinosa acts as a gate control mechanism. As it has been shown (wall 1962; Mendell and Wall, 1964) that although the large fibres are at first very potent in activating the T cells, this effect is later diminished by an inhibitory process. Small fibres have excitatory effect. Continuous nerve impulses transmitting primarily by small fibres, keep the gate comparatively open. Spin stimulation evoke the valley of impulses in which large fibres activity predominates. The T cells are activated, but due to a inhibitory process, the gate is party closed. Sustained stimulation activates small fibre system, while adoption occurs in large fibres. Thus the gate is opened and the outflow of impulses from T cells is increased.

Central efferent fibres influence the gate control mechanism through emotion or previous experience in the form of 'central control trigger' mediated by dorsal column (Hagbarth and Kerr, 1954; Wall, 1967).



Gate Control Theory of Pain

- L - Large diameter fiber
- S - Small diameter fiber
- T - First central transmission cell

MANAGEMENT OF POST OPERATIVE PAIN

The management of pain is still a partially solved problem. The planning of treatment depends upon the cause of pain, nature of the cause, age and psychosomatic behaviour of the patient. There are following different methods of post operative pain relief :

1. Systemic drugs

- Oral & parenteral opioids
- Patient controlled analgesia with opioid
- NSAIDS

2. Regional anaesthesia

- Spinal
 - Local anaesthetic agents
 - Opioids
- Epidural
 - Local anaesthetic agents
 - Opioids
- Patient controlled epidural
- Combined spinal & epidural

3. Nerve blocks

- Peripheral nerve blocks (Brachial, wrist, sciatic, femoral, ankle)
- Intercostal nerve block

4. Subcutaneous infiltration

- Intra articular analgesia
 - Local anaesthetic
 - Opioids

6. Cryo analgesia

7. Transcutaneous nerve stimulation (TENS)

Opioids produce analgesia primarily as a result of their agonist effect on opioid receptor in the CNS. Various routes of administration are available like intravenous, intra muscular, oral, transdermal, sublingual or subcutaneous. There are various opioid drugs available like morphine, meperidine, pentazocine, Nalbuphine, buprenorphine, fentanyl, sefentanil, alfentanil. Opioids cause respiratory depression, Nausea, vomiting, pruritis, constipation, urinary retention, muscular rigidity, addiction potential. In Present study fentanyl is used, it is 100 times more potent than morphine with good cardiovascular stability, shorter half life and no addiction potential. Infusion doses of fentanyl have caused ventilatory depression, in this study single dose of I.V. fentanyl has been used and its analgesic effect are studied. "Andrews and Colleagues" defined the ventilatory depressant effect in awake human of infusion doses of fentanyl.

Opioids can be used through intra thecal or epidural route. Studies by "Behar & Colleagues" (Lancet 1: 527, 1979) have showed the beneficial effects of opioids given by intrathecal or epidural route. This is an effective route for perioperative pain control and duration of analgesia can be increased by long acting drugs or by placement of an epidural catheter. Studies of "Cousins MJ, Mather EL" (Anaesthesiology 61 : 276, 1984) and of "Stenseth R, Sellevold O, Breivik H" (Acta Anaesthesiol Scand 296148, 1985) have showed the effects of intraspinal opioids. "Wang JK, Nauss LA, Thomas JE (Anaesthesiology 50 : 149, 1979) have studied pain relief by intrathecally applied morphine in man. "Chadwick HS, Ready LB" (Anaesthesiology 68 : 925, 1988) have compared the post cesarean analgesic effects of intrathecal and epidural morphine. "Miwa Y, yonemura E, Fukushima K" (Can. J. Anaesh 43 : 907, 1996) have studied the effects of epidural buprenorphine in perioperative period.

Patient controlled analgesia is newer and good concept for post operative pain relief. The self administration of small doses of opioids by patients when they experience pain was originally conceived and developed to minimize the effects of pharmakokinetic and pharmakodynamic variability among individual patients. "Bennett and Colleagues" observed that most patients could titrate themselves to a state of analgesia with minimal redation". "Tamsen et al; showed high success rate of PCA in controlling post operative pain. "Forrest WH, Smethurst PWR, Kienitz ME" (Anaesthesiology 33: 363, 1970) studied the effects of self administered intravenous analgesics. Various drugs which can be used for PCA are

morphine, meperidine, methadone, hydromorphone, oxymorphone, fentanyl, sufentanil, alfentanyl, pentazocine, Nalbuphine, buprenorphine.

The size of bolus and lock out interval are different for different drugs. "Ellis R. Haines D, Shah R" (Br. J. Anaesth 54 : 421, 1982) studied the pain relief after abdominal surgery doing comparison between I.M. morphine, sublingual buprenorphine and self administered I.V. pethidine "Welchew EA" (Anaesth 38 : 19, 1983) have worked on double blind comparison of on-demand intravenous fentanyl with regular intramuscular morphine. "Fleming BM, Coomb DW" (J. Pain Symptom Manage., 7:463, 1992) did a survey of complications documented in a quality control analysis of patient-controlled analgesia in the post operative patient. "Etches RC" (Can. J. Anaesth. 41:125, 1994) studied the respiratory depression associated with patient controlled analgesia. "Parker RK, Holtmann B, White PF"; (Anaesthesiology 76:362, 1992) studied the effect of nighttime opioid infusion with PCA therapy on patient comfort and analgesic requirements after abdominal hysterectomy.

Intra-articular opioids have also been used. Small doses of intra-articular morphine have been administered in an attempt to provide analgesia following arthroscopic and other joint surgery. "Khoury GF, Chen CAN, Garland DE et al, (Anaesthesiology 77:263, 1992) studied the effect of intra articular morphine, bupivacaine, and morphine / bupivacaine for pain control after knee videoarthroscopy. Work of "Joshi GP, Mc Carroll SM, Mc Swiney M et al;" (Reg. Anaesth. 18:245, 1993) studied the effects of intra articular morphine on analgesic requirement after anterior cruciate ligament repair.

Combined spinal – epidural technique with local anaesth. mixture is also a technique for postoperative analgesia. Advantage of this technique in the operating room is rapid onset of surgical anaesthesia obtained with an initial subarachnoid local anaesthetic injection followed by availability of an epidural catheter for ongoing post-operative analgesia.

Opioid and local anaesthetic mixture are used in epidural anaesthesia. "Kehlet and colleagues showed that addition of morphine to a continuous epidural infusion of bupivacaine prevented the development of acute tolerance. Studies by "Cooper et al", and "malin et al;" showed the beneficial effects of diamorphine and bupivacaine mixture for post-operative pain relief.

The main advantage of combining a local anaesthetic with an opioid for epidural for post-operative pain relief are –

- The synergistic analgesic effects of the opioid allows lower concentration of local anaesthetic to provide a prolonged duration of effective analgesia.
- The local anaesthetic provide segmental blockade of somatic sensory fibres, allowing suppression of pain arising during movement, coughing and deep breathing.
- The opioid is synergistic and effective in suppressing visceral pain mediated by 'C' fibres.
- By limiting the volume of local anaesthetic, the addition of opioid assist in minimizing adverse haemodynamic complications.
- Decreased doses of opioid causes less ventilatory depression & other adverse effects of opioids.

Subcutaneous infiltration of local anaesthetic solution produces effective analgesia. A single injection of 0.25 percent bupivacaine into incision line after inguinal hernia repair produces effective analgesia. The side effects of systemically given drugs are also not there through this route. "Hashemi K, Middleton MD" (Ann. R. Coll. Surg. Engl. 65:38, 1983) studied the effects of subcutaneous bupivacaine for post-operative analgesia after herniorrhaphy .

Patient controlled epidural analgesia technique is an effective way for relief of post operative pain. " Chrubasik et al" (Anaesthesiology 1988;68 : 929-933) compared the effectiveness of several epidural opioids administered on demand. They found that the self-administered dose of morphine required to provide analgesia was significantly less than amounts required by continuous epidural infusion or by intravenous PCA. "Sjostrom et al", (Br. J. Anaesth. 60:358, 1988) also reported the use of morphine via PCEA. The fentanyl is also successfully used through this route. "Yarnell RW, Polis T, Reid GN et al" worked on patient controlled analgesia with epidural meperidine after elective cesarean section. "Cohn S. Amar D, Pantuckc et al "; (Anaesthesiology 78:486, 1993) shown the effects of epidural

patient controlled analgesia after cesarean section while using buprenorphine – 0.015% bupivacaine with and without epinephrine.

Nonsteroidal antinflammatory drugs act principally through inhibition of prostaglandin synthesis. Advantage over opioids include a reduction in opioid related side effects, especially respiratory depression, absence of tolerance or addiction potential. But NSAIDS can not replace opioids completely for severe post operative pain, so they are best considered as adjuncts to opioid therapy.

Cryoanalgesia :- Cooling peripheral nerves to temperatures between -5 to 20° C cause disintegration of axons and break down of myelin sheath while the perineurium and epineurium remain intact.

This method utilize CO₂ or N₂O (Nitrous oxide) gas. "Joucken K, Michel L, Schoevaerdts J et al" (Acta Anaesthesiol Belg. 38:1179, 1987) had shown the effects of cryo for post thoracotomy pain relief. "Wood GJ, Lloyd JW, Evans PJ et al", (Lancet 2:249, 1979) had shown the effects of cyro analgesia in day care herniorrhaphy.

Transcutaneous electrical nerve stimulation (TENS) :- It is widely used to manage chronic pain and can be used to provide peri and post operative analgesia. Advantage include absence of opioid induced side effects such as respiratory depression, sedation, nausea & vomiting and urinary retention. "Tyler E, Caldwell C, Ghia JN" (Anaesth. Anal. 61:449, 1982) studied the effects of TENS in management of post operative pain. "Morgan B, Jones AR, Mulcahy KA et al" studied the role of TENS during shoulder distention arthrography.

Nerve Blocks :- Various nerve blocks can be implied for management of post operative pain. Nerve blocks are also effective in the management of chronic pain and pain of terminal cancer. Studies of "Cousins MJ, Bridenbaugh PO" (Anesthesiology 61:276, 1984) have showed the effect of neural blockade in clinical anaesthesia and management of pain. "Selander D", (Acta, Anaesthesiol Scand 21:324, 1977) studied the effect of Catheter technique in axillary plexus block. "Smith BE, Fischer HBJ, Scott PV", (Anaesthesia 39:155, 1984) showed the effects of continuous sciatic nerve block.

PRE-EMPTIVE ANALGESIA

The issue of pre-emptive analgesia has been extensively reviewed by numerous expert authors in several journals. The aim of modern anaesthesia is to ensure that patients having surgery, awake from anaesthesia with excellent pain control and maintain this control throughout the period of convalescence. Aim is to prevent, rather than treat severe postoperative pain. Administering analgesics before the patient emerges from general anaesthesia may result in an ‘acceptable comfort level for the patient in the early postoperative period. This is considered as pre-emptive analgesia. The implication of pre-emptive analgesia extend considerably beyond this. In the practice of pre-emptive analgesia, we attempt to diminish acute pain prior to surgical trauma. Thereby we inhibit the noxious stimuli induced changes in peripheral and central nervous system function that may act to increase and extend post operative pain. Since the “memory” of acute pain is prevented, the duration of analgesia should last longer than the usual duration.

Crill (1913) hypothesized the principles of pre-emptive analgesia, who was a surgeon while working on shock and exhaustion after surgery. Woolf and others developed the scientific foundation upon which the practice of pre-emptive analgesia is based.

Much work has been done in this field and most of them have shown the beneficial effect of pre-emptive form of analgesia in overall post operative outcome. “Bach S, Noreng MF, Tjellden NU” ‘s (Pain 33:297, 1988) work showed the beneficial effect of preoperative lumbar epidural blockade in amputees and phantom limb sensation was greatly reduced. Work of “Kavanagh BP, Katz J, Sandler AN et al, (Can. J. Anaesth. 39:A79, 1992) showed that pain and narcotic use following thoracic surgery are reduced by pre-emptive lumbar epidural fentanyl. “Ejlersen E, Anderson HB, Eliasen K et al” (Anaesth. Analg. 74:495, 1992) studies a comparison between preincisional and post incisional lidocaine infiltration and post operative pain; “Seltzer J, Greek R, Maurer P et al” (Anaesthesiology 79 : A 815, 1993) studied the pre-emptive analgesic effects on regional anaesthesia for shoulder surgery. Work of “Katz J, Clairoux M, Kavanagh BP” (Pain 59:395, 1994) concluded that pre-emptive lumbar epidural anaesthesia reduces post operative pain and patient controlled morphine consumption after lower abdominal surgery. “Salcedo E, Shay P, Berrigan M et al” (Reg. Anaesth. 21,25 : 107, 1996) worked on pre-emptive analgesic efect of interscalene

block prior to shoulder surgery, and found positive results. Work of Johansson B, Glise H, Hallerback B et al, (Anaesth. Analg. 78:210, 1994) studied the effects of pre-operative local infiltration with ropivacaine for post operative pain relief after cholecystectomy. "Woolf CJ, Chong MS" (Anaesth. Analg. 77:362, 1993) worked on pre-emptive analgesia and concluded in favour of treating post operative pain by preventing the establishment of central sensitization.

EPIDURAL SPACE :- The epidural space is the space between the periosteum lining the vertebral canal and the duramater surrounding the canal. Its caphaled extension is till foramen magnum where dura attaches to entire circumference of foramen magnum, caudally it continues with the sacral canal, anteriorly lies the posterior longitudinal ligament, while posteriorily are laminae and ligamentum flavum, lateral limits are marked by the pedicle and intervertebral foramina. What makes the epidural injection safe for the therapeutic and diagnostic administration of drugs, is the anatomy of the space (Pages, 1921; Dogliotti, 1933; Odom, 1940; Cousins, 1945).

The epidural space is not uniform in size and shape throughout. It is triangular and wider in lumbar region (4-6 mm), (Bromage, 1954; Cheng, 1963; Macintosh, 1957). Attempts to pin point the capacity of extradural space were pioneered by Sicard and Foresteir (1921). Lipiodol was injected and the volume was co-related with roentgenographic appearance. Total capacity of 118 ml for extradural space was calculated by Farr (1926) by injecting sodium iodide in fresh cadavers.

The contents of epidural space are fat and loose areolar tissue, through which run the internal vertebral plexus, lymphatics and the dorsal projections, which surround the spinal nerve roots (Bromage, 1954; Cheng, 1963). In third trimester of pregnancy and in cases of large intra - abdominal tumors, the vertebral venous plexus is engorged reducing the size of space as well as the dose of local analgesics (Bromage, 1963-64). The epidural space is a potential space having a negative pressure (Bromage, 1954; Cheng, 1963; Dogliotti, 1933; Heldt, 1928; Janzen, 1926). Only 80% of patients have this negative pressure (Dawkins, 1971).

Identification of epidural space :-

The following points suggest that the needle is in the extradural space.

1. Sudden lack of resistance to advancing needle as it pierces the dense ligamentum flavum.
2. Sudden ease of injection of a little air or liquid from a freely running syringe attached to a needle. If the point is in ligamentum flavum, plunger rebounds, if it is in the space, plunger can be pushed in easily (Sicard and Foerstein, 1922; Dogliotti, 1931).
3. Movement of the bubble on odom's indicator (Odom, 1936), which can be attached to hub of spinal needle.
4. Brooks modification of odom's indicator (Brooks, 1957).
5. Withdrawl of hanging drop of saline on hub of needle (Gutierrez's sign () Gutierrez, 1932).
6. Macintosh spring loaded needle, (Macintosh ; Ibid, 1950), devised by R.H. Salt (Salt, 1963).
7. The Ikle syringe (Ikle, 1950) .
8. The drip indicator (Dawkins, 1961).
9. Ultrasonic localization of lumbar epidural space (Cork et al., 1978).

Tuohy (1945) discovered spinal needle which he claimed could direct a catheter in the desired direction. Henkin et al. (1970) have described a disposable epidural – anesthesia – system which incorporates an external teflon catheter with a precurved tip. The needle tip can be hidden in side the soft catheter tip giving a blunt tipped combination which greatly reduces the chance of accidental dural puncture. Since the catheters are of larger bore than the needle, it allows for reliable aspiration of cerebro spinal fluid and blood and offers no resistance to drug injection . Use of various type of epidural catheters and their methods of sterilization have been described by Davidson et al. (1951). Teflon and vinyl tubing may be auto claved, while polythene tubing should be sterilized with tincture of zephiran.

Epidural block should be performed under strict aseptic conditions, because of possibility of dural puncture (Bromage, 1954).

Fate of drug in epidural space :

The fate of an epidural injection meets primarily diffusion through dura and leakage through intervertebral foramina (mainly in young individuals). Vascular & lymphatic absorption, diffusion through villi and perivascular spaces and uptake in extradural fat mark the other ways of spread (bromage, 1963).

Sicard and Foresteir (1921) injected India ink and lipoidal suspension in an attempt to study the site of action of analgesic solution and noted that these solutions tracked along with the intervertebral foramina and could be traced in the regional lymph glands 10 days after the injection. Odom, (1936) also confirmed that the leakage of solution through each intervertebral foramen was constant and felt that analgesic solution acted at the paravertebral level. Bromage (1957) has produced a following working hypothesis reconciling all the clinical and experimental evidences available for the mode of action of epidural anesthesia.

Lund (1961) observed greater dispersion of radio opaque solution in the older age group, with less leakage of solution through intervertebral foramina. He attributed this to lesser patency of the foramina. Erdemir et. al., (1965) observed that even the weakest co-relation does not exist between the height of the patient and dispersion of solution.

The factors controlling the height of epidural analgesic may be summarized as the site of injection, volume of solution, position of the patient after injection, concentration of solution, pregnancy and intra-abdominal tumor. There is an exaggerated spread of epidural anaesthesia in arterio sclerotic patients. (Bromage, 1962).

The cephalad border of analgesia was determined by Urban (1973), 0.75 to 4 hour following induction of spinal or lumbar epidural anaesthesia. Levels thus obtained followed a straight line best described by the skin intercept of a transverse section through the trunk. There was no difference between spinal and epidural anaesthesia in this regard.

Site of action :- As regards the site of action of extradurally injected solution, it acts in three ways. Firstly, by passing through the duramater, secondly, by affecting the nerves in the paravertebral space and thirdly, at the ink —cuff zones, where dura thins out to become perineurium, permitting the passage of crystalloid molecules and colloidal carbon (Woollam & Millen, 1953). Frumin et. al., (1953) have demonstrated extradural local analgesia in the cerebro – spinal fluid at a different level. Whether this concentration is sufficient for analgesic or not is questionable (Sarnoff and Arrowod, 1946).

OPIATES AS EPIDURAL ANALGESICS :- Postoperative pain following abdominal and thoracic operations was relieved by lignocaine, with the disadvantage of tachyphylaxis. Later long acting drug Bupivacaine was used to give analgesia for 8-12 hours (Moore, 1975; Cromin and Devies 1976). Later, opiates were used as epidural analgesics for chronic as well as acute pain of postoperative period. Behar (1979) first reported the effective use of epidural opioids in humans. The drugs used are morphine 2-3 mg (Behar 1979; Bapat, 1979) ; Pethidine 100 mg (Cousins et al, 1979) and fentanyl 0.1 mg (Wolfe et al; 1979) Behar et. al, (1979) injected 2 mg of morphine for acute or chronic pain, onset of action was 2-3 minutes and effect lasted for 6-24 hours. Bapat (1979) found the onset to be 5 mts. in acute cases and 1 $\frac{1}{4}$ - 2 minutes in chronic cases. The duration of action was 20-40 hour to 15 days in chronic cases. Husemayer et al; (1979) found that 2 mg of epidural morphine was ineffective to provide adequate analgesia in labour. Chagan et al; (1980) tried epidural morphine after caesarean section. They reported that relief of pain was sufficient to substitute surgical anaesthesia.

In the experiment of Gupta et al; (1980) onset remained the same, as in Behar series but the duration was found to be 6 hour to 7 days, while amputees got permanent relief; with the same dosage of epidural morphine.

Rutter et al, (1981) compared the result of morphine, pethidine and fentanyl using them in 2 mg, 50 mg and 0.1 mg dosage respectively. They concluded the results, using a visual linear analogue, pethidine was found to be least effective, morphine largest acting and fentanyl had a relatively shorter duration of action. In all patients, there was a decrease in respiratory rate, but there was no depression of ventilation as judged by changes in PaCO₂.

Epidural fentanyl was first used by Wolfe et al. (1979) in the form of 0.1 mg in 8 ml 0.9% normal saline. Pain relief started in 4-10 minutes and lasted for 200-400 minutes, with a peak action in 20 minutes. No significant alteration in heart rate, blood pressure, respiratory rate or consciousness level was detectable. Bailey and Smith used fentanyl with good results. Rutter et al, (1981) found poor results with 0.1 mg fentanyl with a duration of action of 2 hours. Nalda et al, (1981) used 0.25 mg fentanyl with good results.

Side effects of Epidural Opiates :

Respiratory depression :- Incidence of life threatening respiratory depression has been very low where epidural opioids are used in absence of opioid administration by other routes. It has been reported recently that epidural fentanyl does not cause delayed respiratory depression in volunteers.

Nausea & vomiting :- Bromage et al. observed nausea & vomiting in 50% of subjects approximately 6 hours after epidural morphine. Nausea & vomiting are antagonized by I/V naloxone, without diminishing analgesia.

Urinary retention :- Urinary retention is a more frequently reported complication.

Wolfe and Nicholas, (1979) found complete absence of side effects in their series. Lisandes and Stenquist, (1981) have shown experimentally in cats that fentanyl 0.1-0.5 mg given extradurally abolished or substantially reduced the inhibitory reflex with a latent period of 5 min. or less, thus producing paralytic ileus.

Opioid receptor :- Studies of the binding of opioid drugs and peptides of specific sites and brain and other organs have suggested eight types of opioid receptors. In central nervous system only four major types of receptor have been identified so far (Goldman & Gillam, 1985).

mu (μ) receptors	mediate analgesia
Kappa (K) receptors	mediate analgesia
Sigma (δ) receptors	mediate dysphoria and psychotomimetic effect
Delta receptors	mediate alteration of effective behaviour.

Naloxone has affinity for mu receptors ten-fold higher than for Kappa or delta receptor sites.

Effects mediated by various receptor.

Mu (μ) receptors

- Related to opioid withdrawal syndrome suppression.
- Respiratory depression produced by morphine like drugs.
- Analgesia
- Miosis
- Bradycardia
- Hypothermia
- It decreases skin twitch response to nociceptive stimulus.

Kappa (K) receptors

- Mediate spinal analgesia
- No suppression of higher centres
- No decrease in skin twitch response to nociceptive stimulus.

Sigma (Σ) receptors

- Mediate pupillary dilatation.
- Tachypnoea
- Signs and symptoms of mania.

Later on, existence of delta (δ) receptor was proposed based on the relative potencies of various opiod drugs. It is believed that delta and mu receptor co-exist within the same physical receptor complex and endogenous activation of mu receptor, for example, by β endorphin to mediate analgesia, can be regulated depending on whether leu or met - encephalin predominate at the partner delta receptor. Such study have also provided evidence of the existence of subtypes of opioid receptors. Investigations involving naloxone, an irreversible antagonist, two types of new receptors were postulated.

1. Subtype with low affinity for morphine in μ_2 (μ_2) receptor. This mediates respiratory depression (Paternak et al., (1980).
2. Subtype μ_1 (μ_1) receptor which mediate supra - spinal analgesia in rats, catalepsy and prolactin release.

Recently, epsilon receptor have been discovered for B - endorphins.

PHARMACOLOGY OF DRUGS

BUPIVACAINE :

Bupivacaine, a homologue of mepivacaine and chemically related to lignocaine, was reported by Ekenetam et al in 1957. Pharmacological properties were studied by Hene and Brattstand indicated that bupivacaine was about four times as toxic and three times as potent as mepivacaine and long duration of action ranging from 5-16 hours.

Chemistry :- Bupivacaine belongs to amide group of local anaesthetic and has a basic structure termed amino acyl amide. It has a larger side chain of three extra methyl groups on the piperidine ring . This small addition to the side chain is responsible for high **lipid** solubility, increased protein binding and longer duration of action. It is a weak base with Pka equal to 7.74. Therefore, at physiological pH, the concentration of bupivacaine base is high which is responsible for greatly enhanced penetrating power. It is available as a hydrochloride salt. The resulting solution is acidic and pH ranges from 5.87-5.90.

Properties :- Bupivacaine is highly potent and concentration range usually used for continuous epidural block is 0.25-0.5%, suggested maximum dose is 320-400 mg in labour. The onset of analgesia is 15-18 minutes and duration of effective analgesia has been calculated as 180 mts. It has been used for all manners of blocks, when prolonged analgesia is required. When given by intermittent injection, tachyphylaxis much less common than lignocaine. For pain relief in labour, it is preferred over other local anaesthetics as it produces low incidence of major block. It is 28% lipid soluble and has high plasma protein binding of about 95%.

Pharmacological action of bupivacaine on various system :-

Locally :- it produces nerve blockade. At low concentration example 0.2% solution used for pain relief during labour, it produces preferential sensory blockade.

Regional Effect :- It causes loss of pain & temperature sensation, touch, motor power and vasomotor tone (in that order) in region supplied by the nerve.

Systemic Effect :- These effects occur either due to systemic absorption or due to accidental intravenous injection. The chief systemic effects are on the cardiovascular system & central nervous system.

Cardiovascular System :- McGregor et al (1986) through animal studies have confirmed that at equi-analgesic dose, bupivacaine is 16 times more cardio toxic than lignocaine and this is enhanced in presence of hypoxia, hypercarbia & acidosis. It produces dose related depression in the myocardial contraction and conduction and reduces cardiac sensitivity to adrenaline. It has been associated with high incidence of ventricular tachycardia, fibrillation and cardiac arrest.

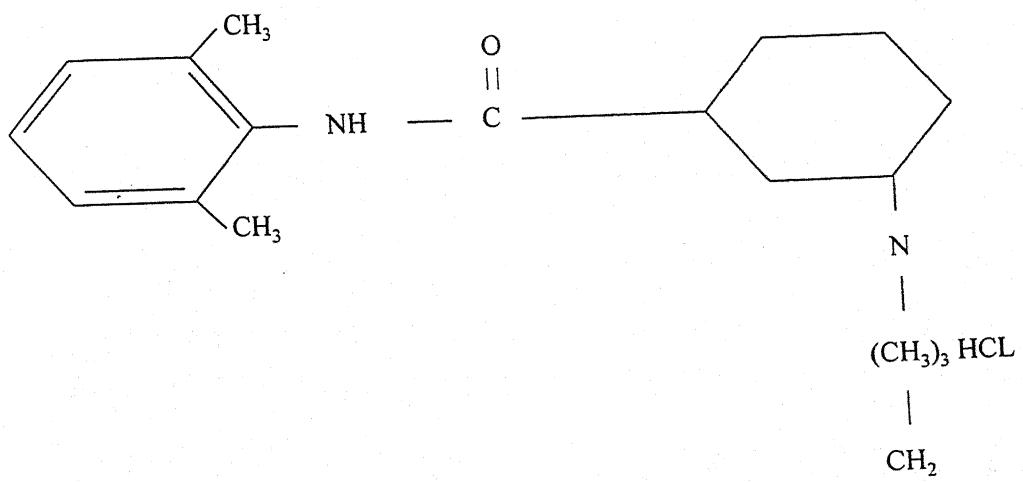
Central Nervous System :- At clinical doses, bupivacaine produces sedation unless rapid absorption occurs into the intravascular space. Rapid intravascular injection causes central nervous system toxicity characterized by numb tongue, circumoral hyperesthesia and tonic-clonic convulsions.

Jorfeldt et al (1968) have shown that toxicity is the function of speed of injection and high serum levels achieved following systemic absorption. Incidence of toxicity is high when dose is more than 1.6 mg / kg.

Tucker, Mather et al, presented a pharmacokinetic data of bupivacaine and found that it is sequestered in certain storage sites (fatty tissue). An initial rapid distribution phase $t \frac{1}{2} (m)$ is 0.46 (± 0.03) indicate hepatic mode of metabolism. Metabolic breakdown commences with removal of piperidine side chain resulting in the product pipocolyl xylidine (PPX). PPX and uncharged bupivacaine are excreted in the urine (Reynold, 1971).

Dosage & Uses Method	% Used	Maximum Safe dose
1. Infiltration	0.25	200 mg
2. Peripheral nerve block	0.25-5.0	200 mg
3. Spinal	0.5	200 mg
4. Epidural	0.25, 0.5	2 mg / kg.

For obstetric purpose 0.125-0.5% solution can be used.



Bupivacaine Hydrochloride

FENTANYL :

Fentanyl citrate is a synthetic phenyl piperidine opioid analgesic and a chemical congener of the reversed ester of pethidine (meperidine). It is primarily a mu (μ) opiate receptor agonist, with an analgesic potency greater than morphine, pethidine or alfentanil. Analgesia is produced principally through interaction with mu receptor at supra spinal sites. Fentanyl also binds, to much lesser degree, to the Kappa (K) opioid receptor located within the spinal cord. The kappa receptor mediates sedation and miosis, but does not affect respiratory rate, heart rate, body temp or gastro intestinal system. It is both potent & safe. The short duration of action of fentanyl is also highly advantageous in the setting of anaesthesia .

Comparative Pharmacological Characteristic of Selected opioids :-

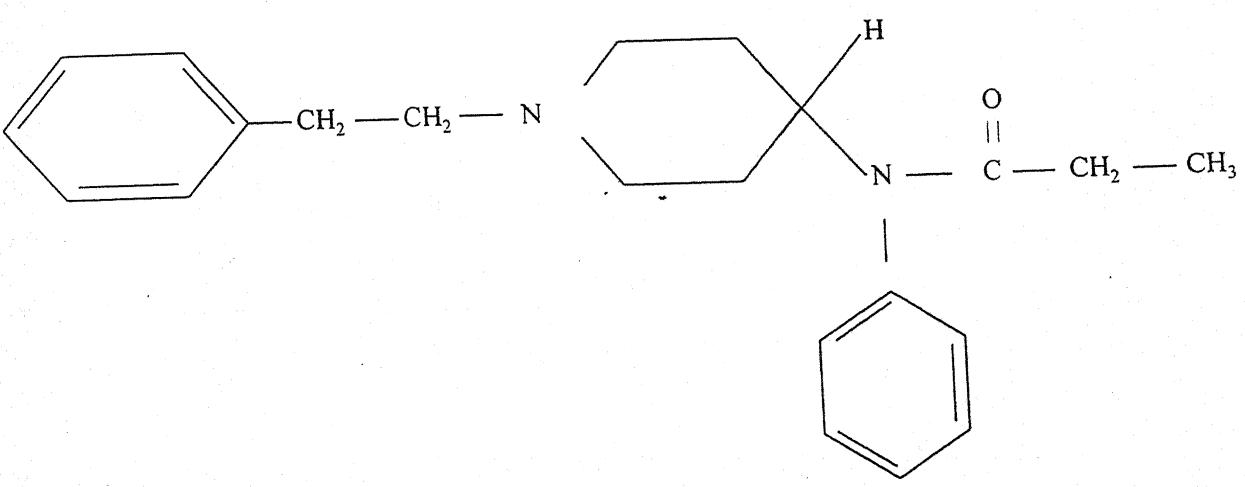
Agent	Analgesic MED ₅₀ (mg/kg).	Anaesthetic dose MED ₅₀ (mg / kg.)	Safety margin
Fentanyl	0.011	0.0012	160
Alfentanil	0.044	0.005	50
Pethidine	6.04	0.45	0
Morphine	3.21	1	33

Distribution :- Fentanyl and its derivatives readily cross the blood brain barriers. It is rapidly distributed to body tissues. The relatively poor blood flow to fatty tissues limits the rate of medications accumulation in these tissues.

Protein Binding :- 80-89%, primarily bound to albumin and lipo proteins; dependent on plasma pH of drugs.

Onset of action :-

- (1) For analgesic effects :- Intramuscular – 7-15 minutes.
 Intranervous – 1-2 minutes.



Fentanyl citrate

(2) Induction doses :- Dependent on rate of administration, 4-5 minutes when administered intravenously at a rate of 400 mcg per minute.

Time to Peak Effect :-

(1) Analgesic Effect :- Intramuscular 20-30 minute
 Intranervous 3-5 minutes

(2) Respiratory depressant effect :-

5-15 minutes following administration of single intranervous dose.

Duration of Action :-

1. Analgesic Effects (anaesthetic adjunct doses)

Intramuscular	1-2 hours
Intranervous	0.5-1 hours (Single dose of upto 100 mg)

The amount of fentanyl which is equianalgesic with 10 mg morphine, is of the order of 0.2 mg (Morrison Loan and Dundee, 1971). While Lee and Alkinson (1977) mention that 0.05 mg fentanyl has the analgesic potency of morphine 10 mg or pethidine 100 mg.

Side Effects : Like other opioids, Fentanyl may produce nausea & vomiting at analgesic doses, by stimulating chemoreceptor trigger zone.

Respiratory depression is marked, apnoea being common with doses in excess of 0.009 mg/kg, can be antagonized by nalorphine and its congeners. It depresses the respiratory centre in the brain stem and decrease respiratory rate, tidal volume, minute ventilation and ventilatory response to carbon dioxide. Fentanyl has little effect on haemodynamic stability (Prys Roberts and Kelman, 1967; Tammisto et al; 1970) and it reduces both cerebral blood flow and cerebral oxygen consumption (Michenfelder and Theye, 1971).

Fentanyl causes alteration in arterial oxygen saturation as observed by "pan PH, James CF, (1994) in their studies on pulse oximetry. "Adams AP, Pybus DA" (1978) also observed delayed respiratory depression after use of fentanyl during anaesthesia, Which is manifested by decrease in arterial oxygen saturation.

Rigidity of the thoracic and abdominal muscles to an extent which makes inflation of lungs difficult, has been reported after rapid intravenous injection of fentanyl (Corssen et al; 1964). This is presumably a manifestation of stimulation of spinal reflexes and, if it occur, if can be abolished by the use of muscle relaxant.

PULSE OXIMETRY

Pulse oximetry is widely available technology that provides easy, non invasive and reliable method to monitor oxygenation, it has become the standards of care in operation theatres and is quickly becoming a routine in recovery rooms, ICU and clinical settings.

As fentanyl causes respiratory depression, so it is essential to monitor arterial oxygen saturation in every patient receiving fentanyl either intravenously or epidurally.

MEASUREMENT AND ASSESSMENT OF PAIN IN ADULTS

Three methods are in common use :

1. Visual analogue scale
2. McGill pain Questionnaire
3. Interactive computer animation.

Visual Analogue Scale (VAS) :- It is the easiest way to measure the intensity of pain. It is simple to use and efficient and can be analysed quickly.

0 = No pain and 10 = worst ever pain.

It could be either horizontal, vertical or curvilinear. An adult places a slide corresponding to the degree of pain they feel. It is a very sensitive way to assess intensity of pain. It assigns a numerical value to pain.

VAS can measure efficiency of analgesia by a particular analgesic by noting the scores before and after treatment.

The main drawback of VAS is that it assumes pain to be unidimensional and measures only the intensity of pain, whereas the nature, location & Psycho – social aspect of pain are not taken into consideration.

AIMS OF STUDY

AIMS OF STUDY

- (1) To study the efficacy of pre-emptive analgesic technique for post operative pain relief.
- (2) To compare the degree and duration of pain relief with different pre-emptive analgesic regimens.
- (3) To evaluate the changes in oxygen saturation with different regimens.
- (4) To study the incidence of complications with these different regimens.

MATERIAL

&

METHODS

MATERIAL AND METHODS

The present study was conducted on patients admitted in various surgical wards in M.L.B. Medical college and hospital, Jhansi, during the year 1998-2001.

Selection of Cases :- The patients selected for study were those kept for surgery by various surgical departments viz general surgery, obstetric & gynaecology and orthopaedics. These patients belonged to ASA grade I and II, of either sex, between the age groups of 21-60 years, undergoing abdominal & lower limb surgery.

A thorough pre-anaesthetic check-up was done in regard of their general condition, cardiovascular and respiratory status and their age, sex, weight and height were recorded. The patients suffering from any neurosurgical disease of either central nervous system or peripheral nervous system and any psychiatric illness were excluded from the study. These patients were subjected to various routine investigations for that age group viz. haemogram, blood sugar, urine for routine & microscopic examination, ECG and chest - x - ray. The procedures and possible risks were explained to the patient and an informed written consent was obtained. These patients were allocated randomly into three groups and their subgroups as follows :-

GROUP I

- (A) Conventional general anaesthetic technique was used and analgesia was provided after complete recovery when patient complaint of pain. (Control group).
- (B) Conventional general anaesthetic technique was used and intravenous fentanyl given after reversal of muscle relaxant.
- (C) Conventional general anaesthetic technique was used and after reversal of muscle relaxant, subcutaneous infiltration of 0.25% solution of bupivacaine along incision line was done.

GROUP II

- (A) Patient received epidural anaesthesia with 15-20 ml of 0.5% solution of bupivacaine (Control group).
- (B) Patient received epidural anaesthesia with 15-20 ml of 0.5% solution of bupivacaine with 50 ugm of fentanyl .

Premedication :-

In group I (A,B,C) :-

- Inj atropine slow intravenous in the dose of 0.6 mg, 5 minutes prior to surgery.
- Inj midazolam slow intravenous in dose of 2.0 mg, 5 min. prior to surgery.
- Inj pentazocine slow intravenous in dose of 20 mg, 5 min prior to surgery.

In group II (A,B) :-

- Inj atropine slow intravenous in dose of 0.6 mg immediately before performing epidural block.
- Inj midazolam slow intravenous in dose of 2.0 mg 10 min. before performing epidural block.

Anaesthetic Technique :- Each patient was reexamined thoroughly before conduct of anaesthesia. Necessary monitoring devices were connected to the patients. Pulse rate, blood pressure, respiratory rate, tidal volume, color of skin and arterial oxygen saturation were recorded.

Group I (A,B,C):- Patients were placed in supine position and after establishing an intravenous line with 18 gauge I.V. Canula, they were premedicated with predecided drugs for that respective group.

- Preoxygenation was done for about 3-5 minutes.
- Induction was done with thiopentone sodium slow I.V. in dose of 4-5 mg / Kg. body weight.
- Intubation was done under the effect of ~~suxamethonium~~ in dose of 75 mg I.V. Stat.
- Maintenance of anaesthesia with vecuronium bromide in loading dose of 4 mg slow I.V. and maintenance with one fifth of that and nitrous oxide, oxygen mixture in concentration of 60-40.
- Reversal was achieved with neotigmine 2.5 mg & glycopyrrolate mix 0.4 mg slow I.V.

In group I_B – After reversal of muscle relaxant, I.V. fentanyl in dose of 50 ugm given.

In group I_C – After reversal of muscle relaxant, subcutaneous infiltration of 0.25% solution of bupivacaine done along the line of incision.

Group II – In operation theatre, an intravenous line was established with 18 gauge I.V. canula. Patients were premeditated with predecided drugs. Then patients were made to lie down in lateral position. Taking all aseptic precautions, epidural space was located at L₃₋₄ or L₄₋₅ intervertebral space. With the help of Tuohy needle and air filled 5 ml syringe. 2 ml of 0.5% bupivacaine was injected a test dose, 5 minutes after which, 16-18 ml of solution with or without fentanyl was injected, according to control and study group. Skin puncture was sealed with tincture benzoin and patient was turned into supine position. The onset of analgesia was evaluated and when the block was established, surgery was allowed to proceed. During the procedure, height of sensory and motor block was also assessed.

Measurement and Assessment :- All the parameters were monitored and assessed by the same person in pre, peri and post operative period. Continuous monitoring of pulse rate, blood pressure respiratory rate, tidal volume and arterial oxygen saturation was done throughout perioperative period and readings were recorded at following time interval.

- Before premedication
- After premedication
- At induction

- Immediate post-operative period.

Post - Operative follow up :- The patients were shifted to recovery room attached to operation theatre and watched post operatively. The pulse rate, blood pressure, respiratory rate, tidal volume, arterial oxygen saturation were recorded.

The patients in the preoperative period were showed the linear analouge scale and trained how to tell about the intensity of their pain co-relating with that scale, and with the help of this mean pain scores were obtained.

All clinical parameters and pain scores were recorded at an interval of $\frac{1}{2}$ hour, 1 hour, 6 hour, 12 hour and 24 hour post-operatively. Complications specially nausea, vomiting, prusitis, urinary retention and muscular rigidity were looked for during the total period of observation and were treated appropriately.

Analysis of Data :- To facilitate overall post operative effects of drugs, scoring scheme described by Dundee et al (1962) has been implicated to grade the desired effects and tonic effects on purely clinical basis. The results obtained from two groups were compared using simple statistical methods. The 't' test was used to compare (examine the difference between two groups) and 'P' value was taken from chart of probability.

Statistical Calculation :-

$$1. \text{ mean } x = \frac{\sum x}{n}$$

where x = number of frequencies

n = number of patients

2. Standard deviation (S.D.) – Calculated by following formulae according to the size of sample.

$$(I) \quad SD = \sqrt{\frac{1}{n-1} [\sum x^2 - nx^2]}$$

when sample is small,

where n = number of patients

Σx = sum of frequencies.

\bar{x} = mean

$$(II) SD = \sqrt{\frac{1}{n-1} [\sum f x^2 - n \bar{x}^2]}$$

when sample is large.

Where n = number of patients

f = frequency

\bar{x} = mean

3. Degree of freedom (d.f.) = $n_1 + n_2 - 2$

4. Standard error of mean = $\frac{SD}{\sqrt{n}}$

Where SD = Standard deviation of mean

n = No. of patients

$$5. 't' values = \frac{\bar{x}_1 - \bar{x}_2}{S \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}$$

where $S = \frac{(n_1 - 1)n_1 + (n_2 - 1)n_2}{n_1 + n_2 - 2}$

when the two samples are independent.

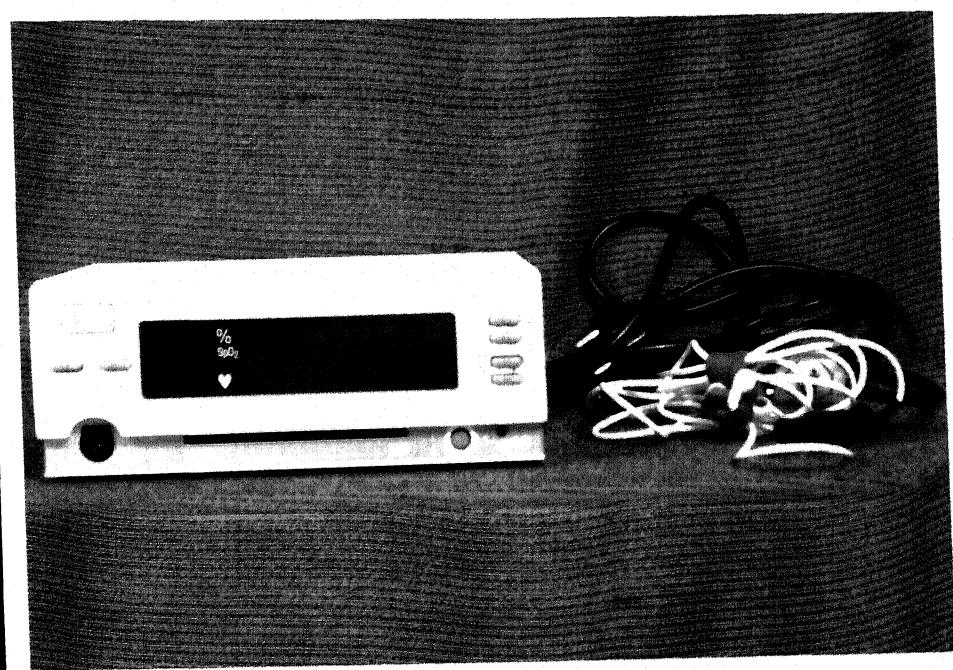
S_1 = SD of one sample

S_2 = SD of other sample

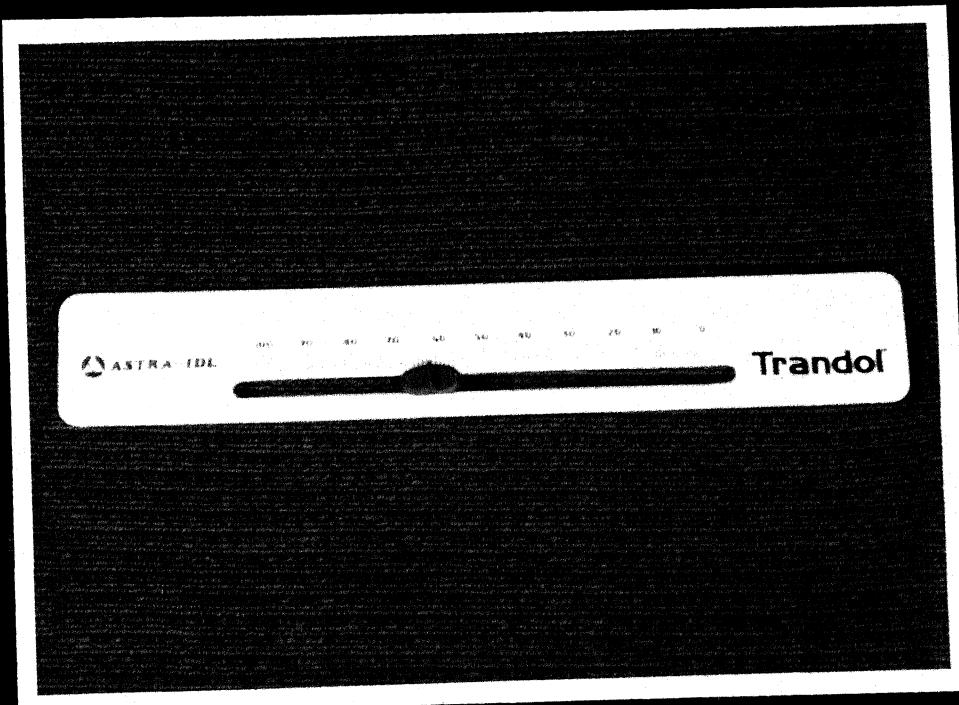
$$'t' value = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{(SE_1)^2 + (SE_2)^2}}$$

(when no. of patients in every group are same)

'P' value = taken from chart of probability.



PULSE OXIMETER



LINEAR ANALOGUE SCALE

OBSERVATIONS & RESULTS

OBSERVATION AND RESULTS

The present work "oxygen saturation and analgesic effects in different pre-emptive analgesic regimen (a comparative clinical study)", has been made on a series of 75 cases admitted in M.L.B. Medical College, hospital, Jhansi. The following observations have been made –

TABLE - 1
Age wise distribution of Cases

Age (in years)	General anaesthesia						Epidural anaesthesia			
	I _A (Control) n = 15		I _B (I.V. fentanyl) n = 15		I _c (S.C. Bupivacaine) n=15		II _A (bupivacaine) n = 15		II _B (bupivacaine with fentanyl) n = 15	
	No.	%	No.	%	No.	%	No.	%	No.	%
20-30	5	33.3	6	40.0	4	26.6	4	26.6	3	20.0
30-40	5	33.3	4	26.6	5	33.3	3	20.0	7	46.6
40-50	4	26.6	3	20.0	3	20.0	5	33.3	2	13.3
50-60	1	6.6	2	13.3	3	20.0	3	20.0	3	20.0
	15	100.0	15	100.0	15	100.0	15	100.0	15	100.0
Mean	35.73		36.13		40.33		42.0		39.33	

Table no. 1 shows that majority of patients were between 31-40 years of age. In the control group I_A (General anaesthesia without pre-emptive regimen). mean age was $35.73 \pm$ and 33.3% of patients were in age group of 31-40 years. In group I_B (Pre - emptive analgesia with I.V. fentanyl) mean age was $36.13 \pm$ and 26.6% patients were in age group of 31 – 40 years. In group I_c (pre-emptive analgesia with subcutaneous infiltration of bupivacaine) mean age was $40.33 \pm$ and 33.3% patients were in age group of 31 – 40 years. In group II_A (Control group with epidural bupivacaine) mean age was $42.0 \pm$ and 20.0% of patients were in age group of 31 – 40 years. In group II_B (epidural bupivacaine with fentanyl) mean age was $39.33 \pm$ and 46.6% patients were in age group of 31 – 40 yrs. There is no statistically significant difference in mean age of five groups.

TABLE - 2**Sex, mean height and weight of different groups**

Group	Sex ratio	Mean height (cm)	Mean weight (kg)
(n = 15)	M : F	Mean \pm SD	Mean \pm SD
I _A	11:4	163.0 \pm 1.20	57.8 \pm 0.89
I _B	9:6	160.0 \pm 1.10	57.0 \pm 0.75
I _C	7:8	157.4 \pm 1.80	52.2 \pm 1.00
II _A	7:8	159.5 \pm 1.60	52.1 \pm 1.20
II _B	5:10	156.0 \pm 2.00	50.3 \pm 0.96

Table two shows that mean average height (in cm) in group I_A is 163.0 ± 1.2 in group I_B is 160.0 ± 1.1 , in group I_C is 157.4 ± 1.8 , in group II_A is 159.5 ± 1.6 and in group II_B is 156 ± 2.0 . The mean weight (in kg) in group I_A is 57.8 ± 0.89 in group I_B is 57.0 ± 0.75 in group I_C is 52.2 ± 1.0 in group II_A is 52.1 ± 1.2 in group II_B is 50.3 ± 0.96 .

No statistical difference could be found ($p > 0.05$) in average height and average weight in all five groups. The cases studied in the series were of both sexes, however males predominated being about 52%.

TABLE - 3
Type and number of surgical operation

Type of surgery	GROUPS				
	General anaesthesia			Epidural anaesthesia	
	I _A (control) n = 15	I _B (I.V. Fentanyl) n = 15	I _C (S.C. Bupiv) n = 15	II _A (bupivacaine) n = 15	II _B (bupiv + fentanyl) n = 15
1. General Surgery					
• Orchidectomy	1	-	-	-	-
• Nephrectomy	1	1	-	-	-
• Nephrolithotomy	3	1	-	-	-
• Appendicectomy	1	2	2	2	1
• Gastrojejunostomy	2	2	-	-	-
• Cholecystectomy	3	3	-	-	-
• Pylolithotomy	1	2	-	-	-
• Lumbar sympathectomy	1	1	1	-	-
• VVF repair	-	1	2	-	-
• MFP	-	1	1	1	-
• Herniorrhaphy	-	1	1	-	-
• Cystolithotomy	-	-	-	-	-
2. Orthopaedics	2	-	2	3	3
• 'k' nailing femur	-	-	-	1	1
• Screw fixation (tibia)	-	-	-	-	1
• AM prosthesis	-	-	-	-	1
• DHS for trochanteric #	-	-	-	1	1
• Mac Murry's osteotomy with plating	-	-	-	1	-
• ORIF by DHS	-	-	-	-	-
• Partial Pattlelectomy	-	-	-	1	-
3. Gynaecology					
• TAH	-	-	3	5	4
• Panhysterectomy	-	-	1	-	1
• Vag. Hysterectomy	-	-	-	1	1
• Ovarian cyst excision	-	-	-	-	1

Table 3 shows the distribution of various surgical procedures in different groups. All the surgical procedures were of about same duration. In general anaesthesia group, abdominal operations were predominated and in epidural anaesthesia group lower limb operations were predominated.

TABLE - 4
Changes in pulse rate during intra operative period

Pulse rate values				
Groups	before premedication $n = 15$ Mean \pm SD	After premedication $n = 15$ Mean \pm SD	at Induction $n = 15$ Mean \pm SD	Immediate post operative $n = 15$ Mean \pm SD
I _A	92.1 ± 12.50	88.8 ± 8.60	91.0 ± 8.70	99.3 ± 10.30
I _B	90.1 ± 11.28	85.2 ± 9.06	84.6 ± 8.60	83.6 ± 9.52
I _C	86.2 ± 12.05	82.9 ± 9.65	82.7 ± 8.73	82.2 ± 9.14
II _A	85.6 ± 11.0	84.9 ± 10.2	83.8 ± 10.62	74.7 ± 7.78
II _B	86.4 ± 9.20	84.5 ± 7.59	85.4 ± 9.34	85.0 ± 9.59

Table no. 4 is showing changes in pulse rate during intra operative period. In group I_A, slight increase in pulse rate was observed in immediate post operative period. In all other groups i.e. I_B, I_C, II_A & II_B pulse was settled after premedication and remained so in immediate post operative period.

The values were not clinically as well as statistically significant ($p = >0.05$)

TABLE - 5

Changes in mean arterial blood pressure during intra operative period

Groups	before premedication $n = 15$ Mean \pm SD	After premedication $n = 15$ Mean \pm SD	at Induction $n = 15$ Mean \pm SD	Immediate post operative $n = 15$ Mean \pm SD
G _A	94.1 \pm 5.2	99.4 \pm 6.0	92.5 \pm 3.6	103.2 \pm 6.0
G _B	98.1 \pm 5.0	95.9 \pm 4.6	88.6 \pm 4.2	92.8 \pm 6.2
G _C	85.5 \pm 4.6	96.7 \pm 4.2	79.3 \pm 6.0	94.9 \pm 4.6
E _A	97.2 \pm 3.0	95.1 \pm 3.8	95.1 \pm 4.8	91.2 \pm 4.2
E _B	94.0 \pm 5.4	93.8 \pm 4.6	88.0 \pm 5.0	90.4 \pm 3.8

Table 5 is showing changes in mean arterial blood pressure during intra operative period. In group I_A, increase in this value was observed at immediate post operative period. In group I_B I_c and II_A, II_B values of mean arterial blood pressure did not show any significant change as compared to pre-operative value.

The values were not clinically as well as statistically significant ($p = >0.05$)

TABLE - 6

Changes in respiratory rate during intra operative period

Groups	before premedication n = 15 Mean ± SD	after premedication n = 15 Mean ± SD	at Induction n= 15 Mean ± SD	Immediate post operative n = 15 Mean ± SD
I _A	17.6 ± 1.20	16.1 ± 1.10	16.0 ± 1.30	18.7 ± 1.28
I _B	16.4 ± 1.00	15.4 ± 1.40	14.9 ± 0.90	14.0 ± 0.86
I _C	17.0 ± 1.40	16.0 ± 1.00	15.3 ± 0.86	14.8 ± 0.96
II _A	15.8 ± 1.60	15.6 ± 1.60	14.7 ± 1.30	13.9 ± 0.88
II _B	16.5 ± 0.92	15.6 ± 1.80	15.3 ± 1.26	13.6 ± 0.98

Table 6 shows changes in respiratory rate per minute during intra operative period. In none of the groups, significant change could be observed as compared to pre – operative values.

The values are not clinically as well as statistically significant ($p = >0.05$).

TABLE - 7**Changes in tidal volume during intra operative period**

Groups	before premedication $n = 15$ $\text{Mean} \pm \text{SD}$	after premedication $n = 15$ $\text{Mean} \pm \text{SD}$	at Induction $n = 15$ $\text{Mean} \pm \text{SD}$	Immediate post operative $n = 15$ $\text{Mean} \pm \text{SD}$
I _A	475.3 \pm 0.62	464 \pm 0.96	458.0 \pm 1.00	456.6 \pm 0.86
I _B	470.7 \pm 0.86	451.4 \pm 0.88	438.0 \pm 0.96	431.6 \pm 0.92
I _C	468.0 \pm 0.88	467.2 \pm 0.94	458.4 \pm 0.98	450.0 \pm 1.20
II _A	461.2 \pm 0.92	445.3 \pm 0.82	439.0 \pm 0.88	466.0 \pm 0.86
II _B	465.1 \pm 0.86	452.8 \pm 0.86	444.0 \pm 0.86	435.0 \pm 0.98

Table 7 is showing changes in tidal volume during intra operative period. There is slight decrease in tidal volume after premedication in all five groups. There is no significant change in all groups at the time of induction or in the immediate post operative period.

The values are not clinically or statistically significant ($p = >0.05$)

TABLE 8**Changes in arterial O₂ saturation during intra operative period**

Groups	before premedication <i>n</i> = 15 Mean \pm SD	after premedication <i>n</i> = 15 Mean \pm SD	at Induction <i>n</i> = 15 Mean \pm SD	Immediate post operative <i>n</i> = 15 Mean \pm SD
I _A	98.8 \pm 1.20	98.0 \pm 0.88	97.7 \pm 1.20	97.8 \pm 1.20
I _B	98.6 \pm 0.98	97.6 \pm 0.90	97.2 \pm 1.40	97.2 \pm 1.40
I _C	98.3 \pm 0.88	97.4 \pm 0.92	97.5 \pm 0.88	97.1 \pm 0.86
II _A	98.6 \pm 0.86	97.5 \pm 0.94	96.7 \pm 0.92	96.7 \pm 0.96
II _B	98.4 \pm 0.96	97.5 \pm 0.92	97.3 \pm 0.98	96.2 \pm 0.88

Table 8 is showing values of arterial oxygen saturation at different times during intra operative period. The oxygen saturation values are not showing any significant changes in all five groups.

The values are not clinically as well as statistically significant ($P > 0.05$).

TABLE - 9**Changes in Pulse rate during post – operative period**

Groups	At $\frac{1}{2}$ an hr. post operatively $n=15$ $Mean \pm SD$	At 1 hr. post operatively $n=15$ $Mean \pm SD$	At 6 hr. post operatively $n=15$ $Mean \pm SD$	At 12 hr. post operatively $n=15$ $Mean \pm SD$	At 24 hr. post operatively $n = 15$ $Mean \pm SD$
I _A	99.3 \pm 1.60	88.0 \pm 0.68	88.0 \pm 1.60	84.0 \pm 1.40	85.0 \pm 1.20
I _B	76.9 \pm 0.86	94.0 \pm 0.92	74.2 \pm 1.20	73.1 \pm 1.20	73.0 \pm 0.96
I _C	79.6 \pm 0.92	78.2 \pm 0.86	91.0 \pm 1.60	86.0 \pm 0.86	80.2 \pm 0.96
II _A	77.0 \pm 1.80	77.6 \pm 0.88	81.4 \pm 1.32	76.0 \pm 0.86	75.2 \pm 0.88
II _B	84.0 \pm 1.76	82.9 \pm 0.96	83.0 \pm 1.06	86.4 \pm 0.96	82.0 \pm 0.96

Table 9 is showing changes in pulse rate during post operative period at the intervals of $\frac{1}{2}$ an hour, 1 hr, 6 hr, 12 hr and 24 hr. In group I_A slight increase in pulse rate was observed in immediate post operative and $\frac{1}{2}$ hr. post-operatively. After that pulse rate was settled. In group I_B, increase in pulse rate was observed at 1 hr. post operatively after that pulse was settled. In group I_C, increase in pulse rate was seen at 6 hr post-operatively, after and before that the pulse rate was settled. In epidural group II_A, and II_B, no significant change in pulse rate was observed at any time interval post operatively.

TABLE - 10

Changes in mean arterial pressure in post operative period

Groups	At $\frac{1}{2}$ an hr. post operatively $n= 15$ Mean \pm SD	At 1 hr. post operatively $n= 15$ Mean \pm SD	At 6 hr. post operatively $n=15$ Mean \pm SD	At 12 hr. post operatively $n=15$ Mean \pm SD	At 24 hr. post operatively $n = 15$ Mean \pm SD
I _A	96.5 \pm 0.86	90.2 \pm 1.20	88.2 \pm 1.20	82.4 \pm 1.20	82.0 \pm 0.86
I _B	89.9 \pm 0.96	96.5 \pm 0.86	88.0 \pm 1.24	86.3 \pm 1.26	82.2 \pm 0.92
I _C	93.2 \pm 0.82	91.4 \pm 0.92	93.8 \pm 0.86	92.2 \pm 0.86	91.3 \pm 0.98
II _A	90.6 \pm 0.94	90.7 \pm 0.96	92.4 \pm 0.92	88.2 \pm 0.92	86.0 \pm 0.96
II _B	90.3 \pm 1.20	90.1 \pm 1.20	90.4 \pm 0.96	86.4 \pm 0.96	84.2 \pm 1.28

Table 10 – Table 10 is showing changes in mean arterial pressure during post operative period. In group I_A, slight increase in mean arterial pressure was observed at $\frac{1}{2}$ an hour post operatively after that blood pressure was settled. In group I_B, slight increase in blood pressure was seen at 1 hr post operatively, with no significant change at any time of observation.

In group I_C, slight increase in blood pressure was observed at 6 hr post-operatively, without any significant change at any other time of observation. In epidural group II_A and II_B, no significant change in mean arterial pressure observed at any time interval post operatively.

TABLE - 11**Changes in respiratory rate during post operative period.**

Groups	At $\frac{1}{2}$ an hr. post operatively $n = 15$ Mean \pm SD	At 1 hr. post operatively $n = 15$ Mean \pm SD	At 6 hr. post operatively $n = 15$ Mean \pm SD	At 12 hr. post operatively $n = 15$ Mean \pm SD	At 24 hr. post operatively $n = 15$ Mean \pm SD
I _A	15.7 \pm 0.86	15.0 \pm 0.96	13.8 \pm 1.20	14.0 \pm 0.96	14.0 \pm 1.64
I _B	14.3 \pm 0.78	13.9 \pm 0.94	11.0 \pm 1.46	12.2 \pm 1.62	14.0 \pm 0.86
I _C	14.4 \pm 1.20	15.2 \pm 0.86	15.9 \pm 0.86	14.0 \pm 1.02	14.2 \pm 0.96
II _A	14.0 \pm 2.02	14.2 \pm 1.20	14.9 \pm 0.72	13.8 \pm 0.92	14.0 \pm 1.20
II _B	14.2 \pm 0.92	13.2 \pm 1.42	14.5 \pm 0.92	15.0 \pm 0.84	14.2 \pm 1.06

Table 11 – Table 11 is showing changes in respiratory rate during post operative period. In group I_A, no significant change observed in respiratory rate during post operative period. In group I_B, slight decrease in respiratory rate was observed but it recovered after 24 hours. In other groups that is I_C, II_A and II_B, no significant change observed in respiratory rate during post – operative period.

TABLE - 12

Changes in tidal volume during post operative period

Groups	At $\frac{1}{2}$ an hr. post operatively $n = 15$ Mean \pm SD	At 1 hr. post operatively $n = 15$ Mean \pm SD	At 6 hr. post operatively $n = 15$ Mean \pm SD	At 12 hr. post operatively $n = 15$ Mean \pm SD	At 24 hr. post operatively $n = 15$ Mean \pm SD
I _A	456.6 ± 0.86	450 ± 0.96	460 ± 0.78	460 ± 0.84	472 ± 0.78
I _B	429.8 ± 0.92	415.3 ± 0.92	440 ± 0.96	450 ± 0.88	450 ± 0.86
I _C	443 ± 1.06	441 ± 1.20	422 ± 0.98	460 ± 0.86	450 ± 0.92
II _A	431 ± 1.02	431 ± 1.06	427 ± 1.64	440 ± 1.24	442 ± 1.20
II _B	432 ± 1.68	433 ± 1.42	429.3 ± 1.02	428 ± 1.02	450 ± 1.06

Table 12 :- Table 12 is showing changes in tidal volume during post-operative period. In group I_A decrease in tidal volume was there but it was not significant.

In group I_B, significant decrease in tidal volume was observed. In group I_C, no significant decrease was seen. In group II_A and II_B, no significant decrease was observed in tidal volume readings at different time intervals during post operative period.

TABLE - 13**Changes in arterial O₂ saturation during post operative period.**

Groups	At ½ an hr. post operatively n= 15 Mean ± SD	At 1 hr. post operatively n= 15 Mean ± SD	At 6 hr. post operatively n=15 Mean ± SD	At 12 hr. post operatively n=15 Mean ± SD	At 24 hr. post operatively n = 15 Mean ± SD
I _A	97.8 ±1.32	96.2 ±1.08	98.0 ± 0.92	98.4 ±0.92	98.0 ± 1.20
I _B	95.9 ±1.20	94.6 ± 2.00	98.0 ± 0.88	99.0 ± 0.86	98.0 ± 0.62
I _C	97.3 ± 0.84	97.4 ± 1.02	97.3 ±0.96	98.0 ± 1.20	98.2 ± 0.96
II _A	96.8 ± 1.20	96.8 ± 1.32	97.8 ± 1.20	98.0 ± 0.96	98.0 ± 0.94
II _B	96.4 ±1.62	96.5 ± 0.86	97.0 ± 0.96	97.1 ± 0.84	98.1 ± 1.20

Table 13 – Table 13 is showing the changes in arterial oxygen saturation during post-operative period. In group I_A, no significant change in arterial oxygen saturation was observed in post operative period. In group I_B, there was decrease in saturation during immediate post operative and early post operative period but later on no change observed. In group I_C, II_A and II_B, no significant decrease in arterial oxygen saturation was observed at any time interval during post operative period.

TABLE - 14**Onset of analgesia in Cases under epidural anaesthesia**

GROUPS (Epidural)				
Time internal (min.)	II _A (Bupivacaine) n=15		II _B (Bupivacaine+Fentanyl) (n=15)	
	NO.	%	NO.	%
0-5	-	-	1	6.6
6-10	-	-	12	80.0
11-15	2	13.3	2	13.3
16-20	9	60.0	-	-
21-25	4	26.6	-	-
Mean onset ± SD	18.7 ± 0.86		9.06 ± 0.92	

Table 14 :- Table 14 is showing time of onset of analgesia in patients operated under epidural anaesthesia. In group II_A in 2 patients, onset of analgesia was observed within 11-15 minutes, in 9 patients within 16-20 mts and in 4 patients within 21-25 minutes of performing epidural block.

In group II_B, 1 patient achieved analgesia within 0-5 mt, 12 patients within 6-10 minutes and rest of 2 patients within 11-15 minutes of epidural block.

TABLE - 15

Height of sensory and motor block in cases. Under epidural anaesthesia

Dermatomal level	II _A (Epi bupivacaine) n = 15				II _B (bupivacaine + fentanyl) n = 15			
	Sensory		Motor		Sensory		Motor	
	No.	%	No.	%	No.	%	No.	%
T ₆	-	-	-	-	8	53.3	-	-
T ₇	10	66.6	-	-	4	26.6	9	60.0
T ₈	3	20.0	9	60.0	3	20.0	4	26.6
T ₉	2	13.3	6	40.0	-	-	2	13.3

Table no. 15 is showing height of sensory and motor block (manifested as dermatomal level) in patients operated under epidural anaesthesia. In group II_A (epidural bupivacaine), sensory block was achieved upto the level of T₇ in 10 patients, upto T₈ in 3 patients and upto T₉ in 2 patients. As for as motor block is concerned, it was achieved upto the level of T₈ in 9 patients and upto T₉ in 6 patients.

In group II_B (epidural bupivacaine with fentanyl), sensory block was upto the dermatomal level of T₆ in 8 patients, upto T₇ in 4 patients and upto T₈ in 3 patients for motor block, it was upto the level of T₇ in 9 patients, upto T₈ in 4 patients and upto T₉ in 2 patients.

TABLE - 16

Time of first analgesic dose requirement post operatively

Groups	Post Operative Period									
	With in $\frac{1}{2}$ an hr.		With in 1 hr.		Within 6 hrs.		Within 12 hrs.		Within 24 hrs.	
	No.	%	No.	%	No.	%	No.	%	No.	%
I _A	15	100	-	-	-	-	-	-	-	-
I _B	-	-	15	100	-	-	-	-	-	-
I _C	-	-	-	-	15	100	-	-	-	-
II _A	-	-	-	-	15	100	-	-	-	-
II _B	-	-	-	-	-	-	13	86.6	2	13.3

Table 16 :- Table 16 is showing time of first analgesic dose requirement in post operative period in different groups. In group I_A, all the 15 patients required analgesia with in $\frac{1}{2}$ an hour post operatively. In group I_B, all the patients demanded for analgesic agent within 1 hour after surgery. In group I_C, all the patient needed analgesia with in 6 hr after surgery. In group II_A, all the patients required analgesia with in first 6 hour post operatively while in group II_B, 13 patients demanded analgesia with in 12 hour and 2 patients needed within 24 hours post operatively.

TABLE - 17
Mean duration of analgesia

Groups	N	Mean duration (in min) \pm SD
I _A	15	28.0 0.94
I _B	15	52.2 0.86
I _C	15	298.0 0.62
II _A	15	206.0 0.96
II _B	15	594.0 0.88

TABLE 17 :- Table 17 is showing mean duration of analgesia (in min) in different groups. In group I_A, mean duration was 28.0 minutes \pm 0.94. In group I_B, mean duration was 52.2 min, \pm 0.86 in I_C, 298.0 min, \pm 0.62 in II_A, it was 206.0 \pm 0.96 min and in group II_B, the duration of analgesia was 594.0 min \pm 0.88.

TABLE - 18
Pain intensities in various groups (mean pain score)
In Post Operative Period (hours)
Mean Pain Scores

Groups		½	1	2	3	4	5	6	7	8	9	10	12	14	16	18
I _A (N=15)	Mean ± SD	7.10± 0.62	5.0 ± 0.69	2.60 ± 1.20	1.40 ± 0.68	1.40 ± 0.72	.80 ± 0.05									
I _B (N=15)	Mean ± SD	4.25 ± 0.86	6.60 ± 0.84	3.00 ± 0.98	1.24 ± 0.74	0.76 ± 0.62	0.82 ± 0.62									
I _C (N=15)	Mean ± SD	0 ± 0.68	1.20 ± 0.70	1.20 ± 0.96	4.30 ± 1.40	5.60 ± 0.98	4.60 ± 0.98	3.80 ± 0.98								
II _A (N=15)	Mean ± SD	0 ± 0.72	0.86 ± 0.02	0.86 ± 1.32	4.62 ± 1.30	5.20 ± 1.42	5.86 ± 1.10	1.32 ± 0.62	0.76 ± 0.62							
II _B (N=15)	Mean ± SD	0 ±	0 ±	0 ±	0 ±	0 ±	0 ±	2.30 ± 1.20	5.00 ± 2.40	5.25 ± 3.20	5.20 ± 2.40	5.00 ± 2.02	4.60 ± 1.62	1.20 ± 0.96	0.86 ± 0.58	

Table 18 is showing pain intensities in different groups i.e. mean pain scores in post operative period. In group I A, maximum score was at half an hour, in group I B it was at 1 hour, in Ic maximum MPS was at 4 hours. In epidural group II A, MPS was obtained at 5 hours and group II B MPS was at 9 hours in the post operatively.

TABLE - 19

Overall opinion (global rating scale) among patients of different pre-emptive analgesic regimens

Groups

Rating of technique	I _A n=15		I _B n=15		I _C n=15		II _A n=15		II _B n=15	
	No.	%	No.	%	No.	%	No.	%	No.	%
Excellent	-	-	-	-	-	-	-	-	10	66.6
Good	-	-	4	26.6	9	60	7	46.6	5	33.3
Fair	-	-	8	53.3	6	40	8	53.3	-	-
Poor	15	100	3	20.0	-	-	-	-	-	-

Table 19 is showing the overall opinion (Global Rating Scale) about the liking or unliking about a particular pre-emptive analgesic regimen. In group I_A (General anaesthesia control group), all the 100% patients rated the techniques as poor. In group I_B (I.V. fentanyl), 26.6% patient rated the techniques as good, 53.3% as fair and 20% as poor. In group I_C (S.C. infiltration of bupivacaine) 60% labeled the technique as good and 40% as fair. In group II_A (Epidural bupivacaine only) 46.6% patients rated the technique as good and 53.3% as fair. In group II_B (Epidural bupivacaine with fentanyl) 66.6% patients rated the regimen to be excellent and 33.3% as good.

TABLE - 20
**Side effects observed in all groups during preoperative and
post operative period**

Side effects	Groups									
	I _A		I _B		I _C		II _A		II _B	
	no.	%	no.	%	no.	%	no.	%	no.	%
1. Nausea	4	26.6	-	-	2	13.3	2	13.3	3	20.0
2. Vomiting	2	13.3	5	33.3	-	-	-	-	2	13.3
3. Respiratory depression	1	6.6	-	-	-	-	-	-	3	20.0
4. Hypotension	-	-	-	-	-	-	5	33.3	2	13.3
5. Retention of urine	-	-	-	-	-	-	-	-	3	20.0
6. Prusitis	-	-	4	26.6	-	-	-	-	2	13.3
7. Muscular rigidity	-	-	1	6.6	-	-	-	-	-	-
8. Others	-	-	-	-	-	-	-	-	-	-
9. Nil	8	53.3	5	33.3	13	86.6	8	53.3	-	-

Table 20 is showing side effects observed in all groups during perioperative and postoperative period.

DISCUSSION

DISCUSSION

Provision of post operative analgesia has been a great challenge to the anaesthesiologist. It involves pain relief, general well beings and escape from side effects of post anaesthetic complications.

“Pre – emptive analgesia” is new concept in modern anaesthesia approach, very valuable because it gives analgesia before the pain starts, i.e. it breaks the pain cycle, so that the overall analgesic dose requirement is reduced as well as adverse effects of pain are prevented to appear, thus the ultimate surgical outcome is improved. The treatment of post – operative pain remains a low medical & nursing priority as nurses fear of causing addiction, respiratory depression or cardio vascular collapse by narcotics and also they are not able to identify the severity of pain and patients are reticent about admitting to pain. All these factors lead the patients to suffer from post operative pain. So it was thought worthwhile to use the pre-emptive technique of analgesia for post operative relief. Opioids have always been a mainstay for the management of post operative pain. Either they are used via parenteral route or through epidural route.

Infiltration of subcutaneous bupivacaine is easy, effective and economical method of pain relief of post operative period and reduces post – operative complications attributed to excessive sedation produced by narcotic analgesics. Also, the infiltration does not affect the post operative healing of incision.

The present study has been made of 75 patients of both sexes who had undergone surgery under general or epidural anaesthesia and were provided pre-emptive analgesia through different routes as a method of post operative pain relief, which are intravenous and epidural administration of opioid (fentanyl) and subcutaneous infiltration of local anesthetic (bupivacaine). Analysis of various observations made in these patients revealed following results.

Effectiveness of pre-emptive analgesia is not found to have any co-relation with age in the present study which are not in accordance with the studies of “Park house et al (1961)” who found a small but significant fall in analgesic requirement in patients over fifty years of age

in immediate post operative period (which is not significant – $p > 0.05$) probably because the patients were free from pain at that time. These findings are in agreement with “Wolfe et al” (1979), “Kataria et al (1981) and work of “Torda AT, Hann P, Mills G, De Leon G, Penman D” who did not notice any change in blood pressure in their study.

Findings of pulse rate, and MAP during post operative period showed that there was increase in pulse rate in group I_A in immediate post operative period, in group I_B at 1 hour post operatively, in group I_C, at 6 hr. post operatively and in group II_A, at 6 hr. and in group II_B at 10 hour post operatively. These changes are not clinically as well as statistically significant ($p>0.05$).

These findings are in accordance with the findings of “Wolfe et al (1971)” and “Kataria et al (1981). This increase is probably because of appearance of pain at that time in post operative period, so this increase in pulse rate and mean arterial pressure can be taken as an index of pain in post operative period and the increase was settled after providing adequate analgesia.

During intra operative period, in group I_A, respiratory rate before premedication is 17.6 ± 1.20 and in immediate post operative period it was 18.7 ± 1.28 . In group I_A, respiratory rate before premedication is 17.6 ± 1.20 and in immediate post operative period it was 18.7 ± 1.28 . In group I_B, it was 16.4 ± 1.00 and 14.0 ± 0.86 respectively. In group I_C, it was 17.0 ± 1.40 and 14.8 ± 0.96 respectively. In group II_A, the respiratory rate was 15.8 ± 1.60 and 13.9 ± 0.88 respectively and in group II_B, the readings were 16.5 ± 0.92 and 13.6 ± 0.98 respectively before premedication and in immediate post operative period. So, the increase in respiratory rate was seen only in group I_A in which no pre-emptive form of analgesic was given and patients were in pain, in all the other groups no significant change observed in respiratory rate. These findings are in agreement with ‘Wolfe et al (1979)” and “Kataria et al” (1981).

During intra operative period, tidal vol. in group I_A patients before premedication is 475.3 ± 0.62 and in immediate post operative period is 456.6 ± 0.86 . In group I_B, it was 470.7 ± 0.86 and 431.6 ± 0.92 respectively. In group I_C, they were 468 ± 0.88 and 450.0 ± 1.20 respectively. In group II_A, it was 461.2 ± 0.92 and 466.0 ± 0.86 and in group II_B, the tidal

volume is 465.1 ± 0.86 and 435.0 ± 0.98 . So the group I_A, patients showed slight decrease in tidal volume in immediate post operative period. It is probably b/o pain due to which patients were unable to breath deeply and during that time respiratory rate was also increased.,it returned to normal after the analgesic was supplemented. In group I_B (I.V. fentanyl), significant decrease in tidal volume is observed, fentanyl causes decrease in tidal volume, but effect was overcome by the time the effect of fentanyl weaned off. These findings were against the findings of "Wolfe et al" (1979). In all the other groups, that is in I_C, II_A and II_B, no significant decrease ($P > 0.05$) in tidal volume was observed at different time intervals during post operative period. These findings are consistent with the work of "Wolfe et al (1979)" and "Torda TA Hann P, Mills a", (1955).

In post operative period, there is not any significant change, neither clinically nor statistically ($p>0.05$) in tidal volume readings, the findings are in agreement with the findings of "Torda TA, Hann P, Mills G. (1945)".

Arterial oxygen saturation reading during intra operativer period, in group I_A, was 98.8 ± 1.20 before premedication and 97.8 ± 1.20 at immediate post operative period. In group I_B, it was 98.6 ± 0.98 and 97.2 ± 1.40 respectively. In group I_c, it was 98.3 ± 0.88 and 97.1 ± 0.86 respectively. In group II_A, it was 98.6 ± 0.85 and 96.7 ± 0.96 respectively and in group II_B, the readings of arterial oxygen saturation were 98.4 ± 0.95 before premedication and 96.2 ± 0.88 in the immediate post operative period. These readings are not showing any significant change ($p > 0.05$). These findings are in agreement with the work of "Nakamura T, Yokoo H, Hamakarva T" (1992).

In post operative period, in group I_A, no significant change in arterial oxygen saturation was observed. In group I_B (I.V. Fentanyl) the decrease in saturation was noted in immediate and early post operative period. It is probably because of the effect of I.V. fentanyl. This is in agreement with the findings of "Rutter et al (1980)". In all other groups i.e. in group I_C, II_A and II_B, no significant decrease in arterial oxygen saturation was observed except at the times when patients were in pain and hyperventilating, at that time, saturation was slightly decreased but returned to normal range after the analgesia was supplemented. These findings are in agreement with the findings of "Nakamura T, Yokoo H, Hamakawa T" (1992).

In epidural group of patients, onset of analgesia was evaluated and compared between bupivacaine and combination of bupivacaine and fentanyl. Mean onset of analgesia in epidural bupivacaine was 18.7 ± 0.86 min which are in agreement with the studies of "Naulty et al (1986)" (where mean onset was 13.84 ± 0.63 mts) and also comparable with the findings of "Bromage (1980)" and "Magora et al (1980)". In epidural bupivacaine and fentanyl group mean onset was 9.06 ± 0.92 min which is coinciding with the findings of "Behar et al" (1979) where the onset of analgesia was between 2-10 mts. So the onset of analgesia is quicker when we mixed fentanyl with bupivacaine, most of patients obtained analgesia with in 6-10 min. and one patient even obtained with in first 5 min. It may be because of synergistic effects of analgesia between local anaesthetic and opioid as described by "Naulty et al" (1986).

In epidural group of patients, heights of sensory and motor block was also established. In group II_A, 66.6% patients got sensory block upto T₇ and 60% got motor block upto T₈. In group II_B, 53.3% patients achieved sensory block upto T₆ and 60.8% had motor block upto T₇. So both the sensory and motor heights were more in epidural bupivacaine and fentanyl combination as compared with only epidural bupivacaine group. These findings are in agreement with the studies of "Cooper DW, Turner G (1992)" and "Badner NW, Bhandari R, Komar WE (1994)", where height achieved of sensory and motor blocks were more in combination than only epidural local anaesthetic.

All the patients in general anaesthesia control group who did not receive any pre-emptive form of analgesia were comfortable in immediate post – operative period and required analgesic supplementation. All the patients of group I_B demanded for pain relief with in 1 hour after surgery while in group I_C, in whom subcutaneous infiltration of bupivacaine is done, were comfortable in immediate post operative period and analgesic demand was found in first 6 hours of surgery.

Patients of group II_A who were given epidural bupivacaine as anaesthetic remained comfortable throughout the surgery and in immediate post operative period as far as the pain is concerned and started complaining pain with in 6 hour after surgery while patients of group II_B, who were given epidural fentanyl along with bupivacaine demanded for analgesia after 10 hours of surgery.

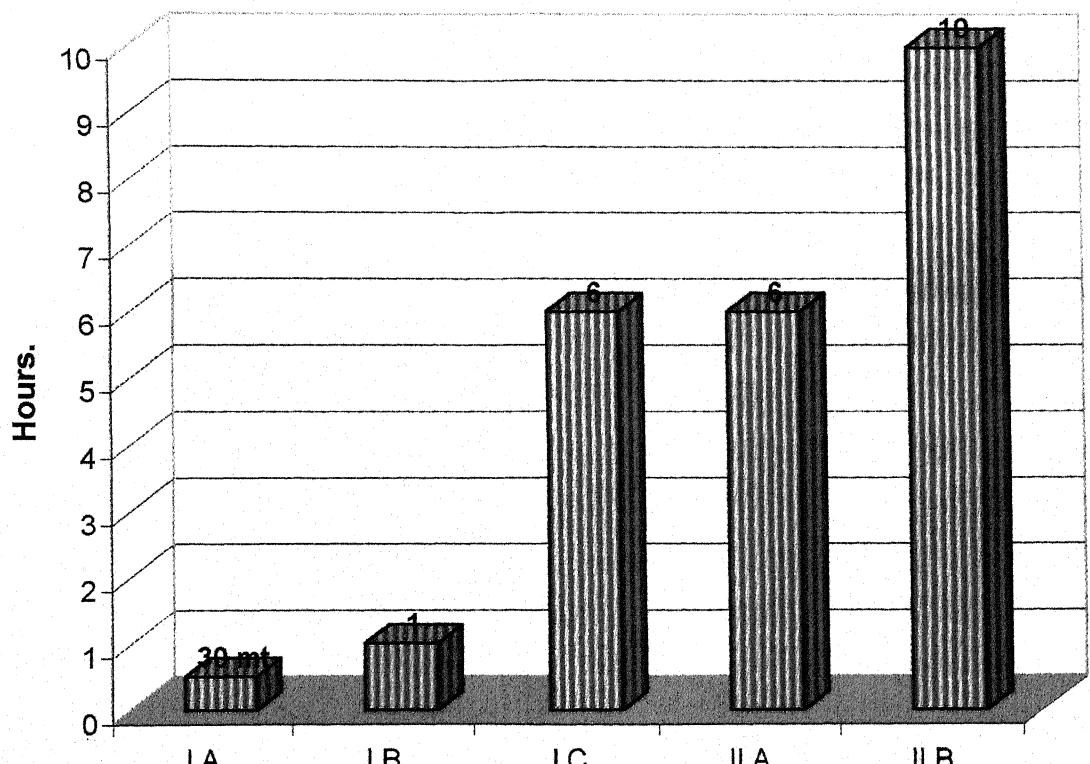
Thus pre-emptive analgesia by every route has a definite role, even I.V. fentanyl given just before recovery showed a quite longer period of pain relief though it is a short acting narcotic analgesic probably because pain cycle was obtunded before it started. Our findings are in accordance with "Rutter et al (1981)" who showed that I.V. fentanyl has shorter duration of action. Patients with subcutaneous infiltration of bupivacaine just before recovery did not complain pain until about 6 hours post operatively. These findings coincided with the studies of "Hashemi K, Middleton MD", who used S.C. bupivacaine for post operative analgesia after herniorrhaphy.

In epidural group II_A i.e. the patients who received only bupivacaine, pain appeared at about 6 hours after surgery. These findings are in agreement with the findings of "Behar et al (1979)" and "Bapat et al (1978, 79)". Maximum duration of analgesia was observed with the combination of epidural bupivacaine with fentanyl which was about 10 hours post - operatively. The longer duration with this combination is also seen by studies of "Naulty et al" (1986) and above findings are also comparable to the observation made by "Bromage (1980)" and "Magora et al (1980)" "Torda TA Hann P, Mills G, D. Leon G, Penmann D". (1995), made the comparison of extradural bupivacaine, fentanyl separately and also in combination for pain relief after abdominal surgery and resulted that pain relief and duration of analgesia was better with the mixture of both the drugs. This finding is co-inciding with the finding of our study.

Mean duration of analgesia in group I_A was 18.0 ± 0.94 min, in group I_B was 52.2 ± 0.86 min, in group I_C was 298.0 ± 0.62 min, in group II_A was 206.0 ± 0.96 and in group II_B, it was 594.0 ± 0.88 min. So it was maximum with the combination of epidural bupivacaine & fentanyl and this is in agreement with the studies of "Torda TA, Hann P" et al. (1995).

In group I_A i.e. patients in whom no pre-emptive form of analgesia was given, maximum Mean Pain Score (MPS) (7.10) were at $\frac{1}{2}$ an hour post operatively, in group I_B (I.V. fentanyl) max. MPS (6.60) were at 1 hour post - operatively, in group I_C, (S.C. bupivacaine) maximum MPS (5.60) were at 4 hour post operatively, in group II_A, (Epidural bupivacaine) maximum PS (5.86) were at 6 hour post operatively and in group II_B (epidural bupivacaine + fentanyl) maximum MPS (5.25) were at 10 hour post operatively. So it is seen that if no pre-

Duration of analgesia between different groups

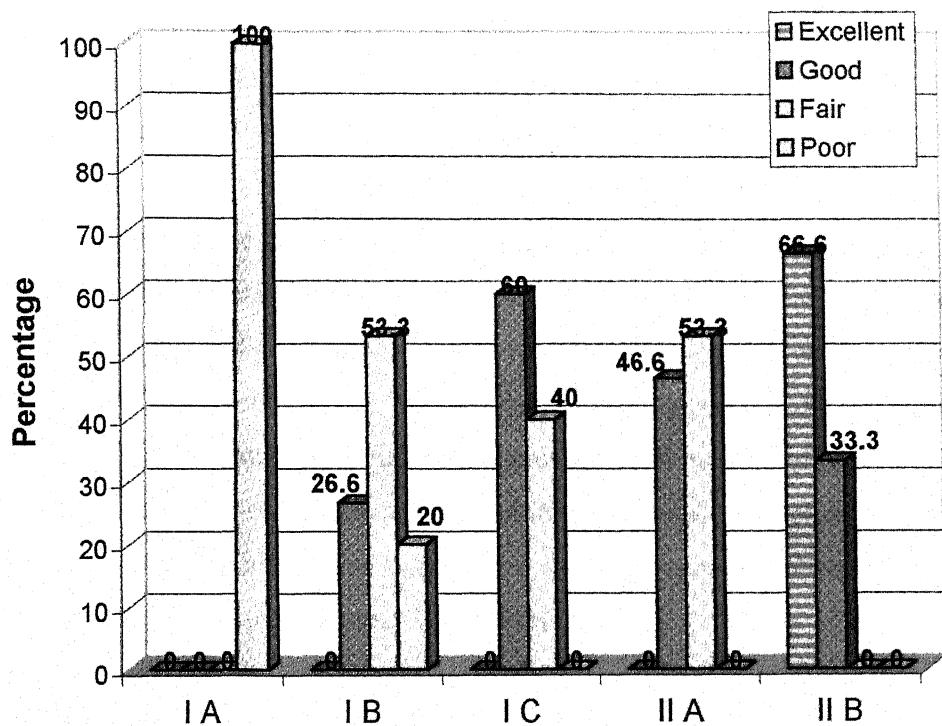


emptive analgesic regimen is utilized then pain scores are very high. "Nakamura T, Yokoo H, Hamakawa T, Takasaki M" (1994, worked on pre-emptive analgesia produced with epidural analgesia and their result suggested that pre-emptive form of analgesia is more effective if the entrance of noxious stimuli into the central nervous system is prevented by pre-incisional epidural block. Also the studies of "Gott Scholk A, Smith DS, Jobes Dr., Kennedy SK" (1998) have concluded that pre-emptive form of analgesia is very effective which decreases post operative pain and is associated with increased activity levels after discharge from the hospital.

Minimum pain scores and intensities were observed with the combination of epidural bupivacaine & fentanyl combination. Duration of analgesia is longest with this regimen. It may be because of synergistic effect of analgesia between local anaesthetic drugs and opioids described by "Naulty et al (1986). Epidural fentanyl may also has longer duration of action because of its lipophilic property (Havell et al, 1977) . Similar observation have also been reported with other opioids like buprenorphine by "Dobkin et al (1977)" and "Kay et al (1978)". Studies of "Cooper DW, Turner G" (1992) on effects of combination of epidural fentanyl and bupivacaine on the treatment of post operative pain concluded that both were addictive in their analgesic action, resulting in decreased requirement of each individual. So the quality of analgesia was found to be best with this regimen, also the supplemented number in post operative period were less as compared to other groups in study. This finding is in agreement with the studies done by "Andrews and Surendran" (1980) where this combination has given good quality of analgesia with longer duration, studies done by "Rutter et al" (1981) have also suggested that fentanyl has very potent response as analgesic are in total agreement in the present study. "Torda TA, Hann P" (1995) also concluded that quality of analgesia is good with the combination of epidural bupivacaine with fentanyl.

Epidural bupivacaine with fentanyl in the present study was found to be at top most on global rating scale since 66.6% of patients rated it as excellent, 33.3% as good and none as poor. Patients who were not provided pre-emptive analgesia i.e. group I_A had maximum no. of analgesia doses requirement in post operative period. The analgesic effects of group I_B, I_C and II_A were in between these two but group I_C patients seemed to be more comfortable than the others and there were less complication in S.C. bupivacaine group of patients.

Overall opinion (global rating scale) among patients for different pre-emptive analgesic regimens



SIDE EFFECTS :- Following side effects are noted in the present study.

Nausea :- A high incidence of nausea was found in patients given epidural fentanyl (20%) but it was still less than the patients not receiving any pre-emptive analgesia (26.6%). In group I_C (S.C. bupivacaine) 13.3% of patients had nausea. These findings co-relate with the work of "Hashemi K, Middleton MD" (1993). In group II_A, 13.3% of patients and in group II_B, 20% of patients had nausea. In "Bapat et al" (1979), with epidural bupivacaine & fentanyl, incidence of nausea reported was 17%, so the findings were comparable with the present study. It also co-incides with the nausea reported with the work of "Hovell (1977)". The incidence of nausea was higher in abdominal surgery cases which may be due to peritoneal stretching during operation.

Vomiting :- In group I_A, 13.3% patients had vomiting. A high % (33.3) of vomiting was found in patients given I.V. fentanyl, which was contrary to the findings of "Reiz et al (1980) who found vomiting in 17% of cases with I.V. fentanyl. The higher rate may be because more of the patients in this group were for abdominal surgeries and peritoneal stretching was responsible for more vomiting post operatively. In group I_C and II_A, none of the patient suffered from vomiting. This finding was comparable with the work of "Rutter et al" (1980)". In group II_B i.e. in epidural fentanyl group, 13.3% patients suffered with vomiting. Stimulation of CTZ at area postrema which appears to posses opioid receptor is considered to be a cause of nausea and vomiting observed with opioid drugs ("Goodman and Gilliman, 1985)". This is also comparable with the vomiting observed with the worth of "Badner NH, Bhandari R, Komar WE (1994)".

Respiratory depression :- In group I_A, I_B, I_C and II_A, none of the patient had respiratory depression. In I.V. fentanyl group, it is probably because the patient were on I.P.P.V. with endotracheal tube and after the end of surgery, with in some time, the effect of I.V. fentanyl was weared off. In S.C. bupivacaine infiltration group, no respiratory depression was coinciding with the findings of "Hashemi K, Middleton MD, (1992) who did not notice any respiratory depression in their study.

In epidural bupivacaine group, no respiratory depression was in agreement with the findings of 'Rutter et al (1981)" and "Wolfe et al (1980)". In combination of epidural bupivacaine

and fentanyl, 20% of patients suffered from respiratory depression post operatively. It is probably because of epidural fentanyl which showed respiratory depressant effect after its delayed absorption from the epidural space. It is in agreement with the findings of "Torda TA, Hann P, Mills G, De Leon G (1995) but contrary to the findings of "Glynn et al" (1979), "Scot and Mc. Clure (1979)", "Boas (1980)" and "Welch (1981)", who noticed no respiratory depression with epidural fentanyl in their studies.

Hypotension :- In group I_A, I_B & I_C, no hypotension seen in any time of observation during intra operative or post operative period. These findings are comparable with "Wolfe et al" (1980), "Rutter et al (1981)" and "Hashemi et al" (1993). In group II_A, 33.3% patients suffered from hypotension and it soon recovered after the treatment was given. This is in comparison with the findings of "Torda TA, Hann P, Mills G, De Leon G, Pen mann D. (1995)." In group II_B (epidural bupivacaine with fentanyl), 13.3% patients suffered with hypotension, the observation comparable with the studies of "Cooper DW, Turner G".

Retention of Urine :- In none of the patient of group I_A, I_B, I_C and II_A, the retention of urine was complaint, the findings in agreement with the work of "Wolfe et al (1980)", "Rutter et al (1981)" and "Bapat et al (1979)". 20% of patients in II_B group had complaint of retention of urine. "Magora et al (1980)", "Reiz et al (1980)" and "Andrews and Surendran" (1981) reported the incidence of retention of urine after epidural opioids. They attribtued it to the increased tone of detrusor muscle and of vesical sphincter, thus impending micturition. The patients were treated by catheterization.

Pruritis :- The complaint of itching was observed in patients who received fentanyl in any form in that in either I.V. fentanyl or epidural fentanyl. The incidence was 26.6% patients in I.V. fentanyl group and 20% of patients in epidural fentanyl group. "Reiz et al (1980)", "Hales et al" (1980) and "Andrews and Surendran" (1981) observed itching in their cases. Also the studies of "Badner NH, Bhandari R, Komar WE" (1994) showed that itching was there with the use of fentanyl. But the findings are contrary to the observation made by "Ilahi OA, Davidson JP, Tullor HS" who stated that pruritis was less common with fentanyl.

Muscular rigidity :- Muscular rigidity was observed in only one case of I.V. fentanyl group, finding in agreement with ⁴Cohen S, Amar D, Pantuck CB, Pantuck EJ, Waissman AM,

Landa S, Singer N" who observed muscular rigidity with the use of fentanyl. It was seen just after fentanyl was given and treated with immediate reintubation which was facilitated by Suxamethonium and patient was kept under I.P.P.V. until the effect of fentanyl weared off. No further complications was noted in that patient after that in whole period of observation in post operative phase.

No other side effects were observed in this study.

CONCLUSION

CONCLUSION

The present study, conducted on 75 patients of both sexes, provided pre-emptive analgesia through different routes. After analysing the observed data, following conclusions were made:-

1. Excellent cardiovascular stability was maintained during post-operative period in patients who utilized "pre-emptive technique" via any route.
2. In each group, respiratory rate and tidal volume, were well maintained within normal range and no significant respiratory depression observed with any technique.
3. Arterial oxygen saturation were maintained with in normal range and there is no significant alteration in oxygen saturation findings during whole peiod of observation in post-operative period.
4. Onset of analgesia was quicker in combination of epidural bupivacaine and fentanyl as compared to only bupivacaine group.
5. Heights achieved for sensory and motor blocks were more with the combination of epidural bupivacaine and fentanyl as compared to epidural bupivacaine only.
6. Among all the pre-emptive regimens utilized for post-operative pain relief, duration of analgesia was maximum with the epidural bupivacaine & fentanyl group of patients, (10 hours) followed by S.C. bupivacaine (6 hours) and then with I.V. fentanyl given just before recovery (1 hour).
7. Maximum mean pain scores and intensities observed with the control group of general anaesthesia as compared to the control group of epidural bupivacaine, in which no pre-emptive analgesic regimens was utilized, while less mean pain scores were there with S.C. bupivacaine and I.V. fentanyl group and least Mean Pain Scores were with combination of epidural bupivacaine & fentanyl.
8. Complications observed are minimum with the S.C. bupivacaine group in which only observed complication was nausea (13.3%). With I.V. fentanyl, vomiting (33.3%), pruritis (26.6%) & muscular rigidity (6.6%). With epidural bupivacaine & fentanyl complication osberved were nausea (20%), vomiting (33.3%) respiratory depression (20%) hypotension (13.3%) & retention of urine (20%).

9. The pre-emptive analgesic technique is effective way of providing post operative analgesia, reduces the adverse effects of post operative pain and improves overall surgical outcome.

So to conclude, epidural bupivacaine with fentanyl was found to give excellent post-operative pain relief in term of both duration and quality, which was followed by S.C. bupivacaine infiltration on incision line, having minimal complication. I.V. fentanyl as pre-emptive analgesic produced excellent pain relief though duration was short lived.

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Oxygen saturation and analgesic effect in different pre-emptive analgesic regimens

(a comparative clinical study)

SUMMARY

FOR

DOCTOR OF MEDICINE
[ANAESTHESIOLOGY]



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SUMMARY

The international association for the study of pain has defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”. The interpretation of pain is subjective. Pain is an unpleasant sensation localized to a part of the body. So pain is not only pain, but also an alarm for body injury.

Post operative pain does not directly cause death but so many adverse effects and morbidity that overall surgical outcome is negatively affected.

The traditional approach to post operative analgesia is to begin therapy when surgery is completed and pain is experienced. But one aim of modern anaesthesia is to ensure that patient have surgery without pain, awake from anaesthesia with excellent pain control and maintains this control throughout the period of convalescence. The aim is to prevent rather than treat severe post operative pain. This concept is known as “*pre-emptive analgesia*”. By this we prevent the establishment of altered central processing which amplifies post operative pain.

There are various modalities of post – operative pain relief. The mainstay for post-operative pain relief since ancient time are systemic opioids. They provide good, effective and long duration of pain relief.

Local infiltration technique is useful as single subcutaneous injection of local anaesthetic can produce sustained pain relief for a period of hours on incision line without altering vital parameters, but its limitation is that, it does not reduce dull aching type visceral pain so is effective only in operations where viscera handling is minimum such as herniorrhaphy appendicectomy etc. and also it can delay in wound healing.

Though much has been said about the pre-emptive analgesia for post operative pain relief but which route should be chosen so as to have maximum pain relief along with minimum oxygen desaturation is still debatable. Therefore it was decided to evaluate the three different routes i.e. intravenous opioid, subcutaneous infiltration of bupivacaine and epidural opioids

for the relief post operative pain along with its effect on arterial oxygen saturation as an index of respiratory depression.

The present work "*oxygen saturation and analgesic effects in different pre-emptive analgesic regimen (a comparative clinical study)*", has been made on a series of 75 cases admitted in M.L.B. Medical College hospital, Jhansi.

The patients selected for study were those kept for surgery by various surgical departments viz general surgery, obstetric & gynaecology and orthopaedics. These patients belonged to ASA grade I and II, of either sex, between the age groups of 21-60 years, undergoing abdominal & lower limb surgery.

These patients were allocated randomly into three groups and their subgroups as follows :-

GROUP I

- (A) Conventional general anaesthetic technique was used and analgesia was provided after complete recovery when patient complaint of pain. (Control group).
- (B) Conventional general anaesthetic technique was used and intravenous fentanyl given after reversal of muscle relaxant.
- (C) Conventional general anaesthetic technique was used and after reversal of muscle relaxant, subcutaneous infiltration of 0.25% solution of bupivacaine along incision line was done.

GROUP II

(A) Patient received epidural anaesthesia with 15-20 ml of 0.5% solution of bupivacaine (Control group).

(B) Patient received epidural anaesthesia with 15-20 ml of 0.5% solution of bupivacaine with 50 ug/ml of fentanyl.

Patients were premedicated and anaesthetized according to the technique chosen. Continuous monitoring of pulse rate, blood pressure, respiratory rate, tidal volume and arterial oxygen was done throughout perioperative period and readings were recorded at following time interval –

- Before premedication
- After premedication
- At induction
- Immediate post operative period

These parameters were also observed during post operative period and pain scores were recorded at an interval of $\frac{1}{2}$ hour, 1 hour, 6 hours, 12 hours and 24 hours postoperatively. Complications specially nausea, vomiting, pruritus, urinary retention and muscular rigidity were looked for during the total period of observation and were treated appropriately.

After analysing the observed data, following conclusions were made :

The present study, conducted on 75 patients of both sexes, provided pre-emptive analgesia through different routes. After analysing the observed data, following conclusions were made:-

1. Excellent cardiovascular stability was maintained during post-operative period in patients who utilized "pre-emptive technique" via any route.
2. In each group, respiratory rate and tidal volume, were well maintained within normal range and no significant respiratory depression observed with any technique.

3. Arterial oxygen saturation were maintained with in normal range and there is no significant alteration in oxygen saturation findings during whole peiod of observation in post-operative period.
4. Onset of analgesia was quicker in combination of epidural bupivacaine and fentanyl as compared to only bupivacaine group.
5. Heights achieved for sensory and motor blocks were more with the combination of epidural bupivacaine and fentanyl as compared to epidural bupivacaine only.
6. Among all the pre-emptive regimens utilized for post-operative pain relief, duration of analgesia was maximum with the epidural bupivacaine & fentanyl group of patients, (10 hours) followed by S.C. bupivacaine (6 hours) and then with I.V. fentanyl given just before recovery (1 hour).
7. Maximum mean pain scores and intensities observed with the control group of general anaesthesia as compared to the control group of epidural bupivacaine, in which no pre-emptive analgesic regimens was utilized, while less mean pain scores were there with S.C. bupivacaine and I.V. fentanyl group and least Mean Pain Scores were with combination of epidural bupivacaine & fentanyl.
8. Complications observed are minimum with the S.C. bupivacaine group in which only observed complication was nausea (13.3%). With I.V. fentanyl, vomiting (33.3%), pruritis (26.6%) & muscular rigidity (6.6%). With epidural bupivacaine & fentanyl complication osberved were nausea (20%), vomiting (33.3%) respiratory depressio (20%) hypotension (13.3%) & retention of urine (20%).
9. The pre-emptive analgesic technique is effective way of providing post operative analgesia, reduces the adverse effects of post operative pain and improves overall surgical outcome.

So to conclude, epidural bupivacaine with fentanyl was found to give excellent post-operative pain relief in term of both duration and quality, which was followed by S.C. bupivacaine infiltration on incision line, having minimal complication. I.V. fentanyl as pre-emptive analgesic produced excellent pain relief though duration was short lived.